UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD., Plaintiffs, v. SANDOZ, INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG, and MOMENTA PHARMACEUTICALS, INC., Defendants.	Civil Action No. 08-CV-7611 (BSJ)(AJP) ECF Case
TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD., Plaintiffs, v. MYLAN PHARMACEUTICALS INC., MYLAN INC., and NATCO PHARMA LTD., Defendants.	Civil Action No. 09-CV-8824 (BSJ) (AJP) ECF Case **DEFENDANTS SANDOZ INC.'S AND MOMENTA PHARMACEUTICALS, INC.'S POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW** **(HIGHLY CONFIDENTIAL AND EXTERNAL COUNSEL ONLY – FILED UNDER SEAL PURSUANT TO PROTECTIVE ORDER)**

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TABLE OF CONTENTS

Page

TABLE OF CONTENTS
(continued)

Page

TABLE OF CONTENTS
(continued)

Page

TABLE OF AUTHORITIES

Page(s)

CASES

TABLE OF AUTHORITIES
(continued)

Page(s)

TABLE OF AUTHORITIES
(continued)

Page(s)

TABLE OF AUTHORITIES
(continued)

Page(s)

STATUTES

Sandoz Inc. and Momenta Pharmaceuticals, Inc. (collectively "Sandoz") appreciate the Court's generous allotment of time and attention to the trial of this matter.

Sandoz presents below its proposed findings of fact and conclusions of law regarding non-infringement based on Teva's failure to prove that Sandoz's marketed product will meet the claim limitations "takes place for a time and at a temperature predetermined by test reaction" and "copolymer-1," and will have a weight average molecular weight below 10 kDa. Sandoz also presents its proposed findings of fact and conclusions of law regarding invalidity based on lack of enablement, indefiniteness, obviousness, and unenforceability due to inequitable conduct. To reduce duplication with Mylan's submission, Sandoz additionally refers to Mylan's proposed findings of fact and conclusions of law, including Teva's failure to prove infringement of the "copolymer-1" molar ratio limitation.

I. SANDOZ DOES NOT INFRINGE THE ASSERTED CLAIMS

A. Findings of Fact on Non-Infringement

1. Sandoz Does Not Infringe Claims 1-3 of the '898 Patent, Claims 1-3 of the '430 Patent, Claim 1 of the '476 Patent, and Claim 1 of the '161 Patent, Because It Does Not Use a Test Reaction to Predetermine Both the Time and Temperature of the Step of Reacting Protected Copolymer-1 With HBr to Form TFA Cop-1

1. The Court construed "predetermined by test reaction" to mean "determined beforehand by a reaction carried out to determine results of varying reaction conditions." (CC Order at 50.) Teva did not challenge the meaning of the claim limitation "takes place for a time and at a temperature."

2. Sandoz and Momenta currently employ an in-process viscometry method to determine the endpoint of their HBr/acetic acid Step 2 depolymerization reaction. (Sept. Tr. 1099:21-23; 1100:25-1101:3; 1103:24-1104:7 (Bishop); PTX 913R.) Dr. Bishop confirmed that

process 1.1.0, Momenta's viscosity method, will be used in the future for determining the endpoint of the depolymerization reaction when producing Sandoz's final glatiramer acetate product. (Sept. Tr. 1105:9-11.)

3. Dr. Laird is currently Owner and Senior Consultant for Scientific Update, a consultancy in the area of organic process chemistry he founded in 1989. Scientific Update has provided consulting for companies such as Merck, Pfizer, Teva and Novartis in the areas of organic synthesis, process development scale-up, crystallization, and solid state forms, among other topics. (Sept. Tr. 1112:25-1113:15, 1114:11-16.)

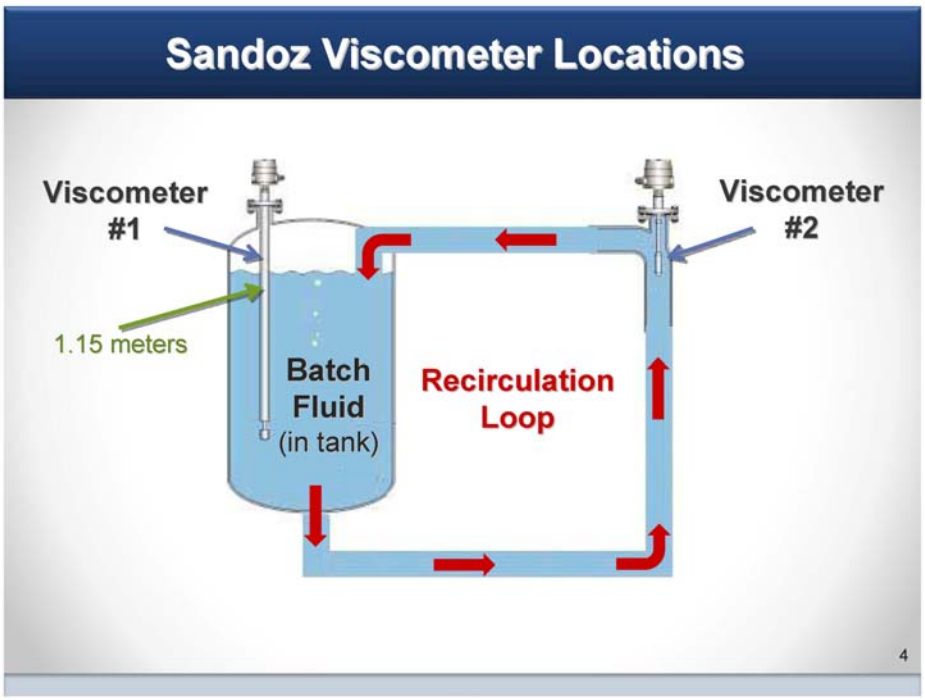
4. Dr. Laird received his Ph.D. in Organic Chemistry from the University of London in 1970. (Sept. Tr. 1117:25-118:7; DTX 1967.) He has been a visiting professor at the University of Sussex since 2004. (DTX 1967.)

5. Previously, Dr. Laird served as head of chemical development for SmithKline and French (now Glaxo Smith Kline) from 1979-1989, where he was responsible for small-scale manufacture of all of Smith Kline's drugs prior to launch. (Sept. Tr. 1116:20-1117:6.) He currently serves on the advisory board for Sand Chemicals, a peptide and polypeptide manufacturer in Switzerland. (Sept. Tr. 1117:16-22.)

6. Dr. Laird has served as editor of the peer-reviewed journal "Organic Process Research & Development," published by the American Chemical Society, since 1995. (Sept. Tr. 1119:1-20.)

7. Dr. Laird testified that Sandoz's in-process method uses a viscometer to continually measure the viscosity of its intermediate-1 product during the Step 2 reaction. (Sept. Tr. 1136:12-21.) Referring to the diagram below, Dr. Laird explained that a viscometer is inserted into a tank in which the depolymerization reaction takes place, where it "measures the

viscosity and also measures the temperature very accurately at the same point at which the viscosity is measured." (Sept. Tr. 1131:14-23; DTX-3580, at 4.) A second, back-up viscometer is inserted into a recirculation loop, where it also measures both temperature and viscosity at a different location in the reaction tank from the first viscometer. (Sept. Tr. 1131:24-1132:3; DTX-3580, at 4.)



(DTX 3580, at 4.)

8. During the reaction, the operator continually compares the viscometer readings with a chart of previously-determined correlations between viscosity, temperature, and molecular weight. (Sept. Tr. 1132:10-16, 1135:9-17.) Once a particular viscosity and temperature correlated with the desired molecular weight is reached, the operator stops the reaction by adding water to the reaction mixture, also called "quenching." (Sept. Tr. 1132:17-1133:2, 1133:10-24.)

9. The viscosity readings taken during the Step 2 process measure "resistance to flow," and are not reactions. (Sept. Tr. 1130:1-6; 1132:4-9.) The viscometers are measuring a

physical property of the solution that is related to the progress of the depolymerization reaction. (Sept. Tr. 1132:6-9.) The experts agree that the endpoint of the Step 2 reaction is triggered when the viscosity reaches a certain level, rather than at a specific predetermined time. (Sept. Tr. 514:4-12; 516:10-19; 519:4-11 (Gokel); Sept. Tr. 1138:2-7 (Laird).)

10. Dr. Bishop testified that because Momenta's viscometry method proved to be successful, Momenta does not plan to use the "backup" method it had developed to determine the optimal reaction time based on measuring the average temperature during the depolymerization step in the reactor. (Sept. Tr. 1105:12-1106:3.) This method was also called the "average temperature methodology." (Sept. Tr. 1105:16-21.) Momenta did not use the average temperature methodology to prepare batches of its glatiramer acetate product. (Sept. Tr. at 1108:13-1109:1 (Bishop); 1167:99-21, 1159:5-11 (Laird).) Going forward, Momenta will use a second viscometer as a "backup" to the main viscometer. (Sept. Tr. 1106:4-14.)

11. Dr. Gokel initially testified that Sandoz and Momenta predetermined a relationship between time, temperature and viscosity that was used to determine the endpoint for the Step 2 reaction. (Sept. Tr. 434:9-17.) But he agreed that a viscometer does not measure time (Sept. Tr. 516:20-22), and admitted that the endpoint of the depolymerization reaction is reached without reference to the time of the reaction:

> Q. And what I'm asking you, sir, is about the step 2 reaction of Sandoz using the viscometer method, and when that reaction ends. And that reaction ends when the specific viscosity level is reached that correlates with a specific preset temperature, correct?
>
> A. The way the batch records are set up, the operator is told to end at a particular viscosity that correlates with a particular temperature.

(Sept. Tr. 519:4-11.)

12. Dr. Gokel also admitted that, when performing Momenta's Step 2 process, there would be no way for the operator to know with complete certainty that, after a certain time period, a set viscosity level would be reached:

> Q. Yes, but my question is, talking about the operator, running the reaction, and you agree with me that the operator cannot just set this alarm clock that you mentioned and leave for 30 hours and come back with complete certainty that the viscosity level associated with a particular temperature has been reached, can she?
>
> A. Not with complete certainty. (Sept. Tr. 519:19-25.)

13. Thus, Teva failed to satisfy its burden to prove that Sandoz's proposed product infringes claims 1-3 of the '898 Patent, claims 1-3 of the '430 Patent, claim 1 of the '476 Patent, and claim 1 of the '161 Patent, which all require "reacting protected copolymer-1 with hydrobromic acid . . . for a time and at a temperature predetermined by test reaction." (PTX 3-5.)

2. Plaintiff Did Not Show That Sandoz's Proposed Product Has a Molar Ratio of Approximately 6:2:5:1 as Required by All of the Asserted Claims

14. The proposed findings and conclusions in Mylan's separate filing concerning Teva's failure to prove its product has a molar ratio of 6:2:5:1 also apply to Teva's failure of proof on this point with respect to Sandoz's proposed product.

15. The molar fractions for Sandoz's lot 051M7282 were 0.427 for alanine, 0.344 for lysine, 0.136 for glutamic acid, and 0.092 for tyrosine. (Sept. Tr. 1194:20 – 1195:9 (Bishop); PTX-913-R, page 28 of 63, Table 6.) Like Mylan's proposed product, batches made under Sandoz's current 1.1.0 specifications deviate from the molar ratio 6:2:5:1 by having over 30% more tyrosine than "copolymer-1" as it is defined in the patents. (*See* Sept. Tr. 491:16-492:6 (Gokel); 715:3-8, 777:4-15 (Kent).)

16. The molar fraction for tyrosine in Mylan's proposed product is .092. (Sept. Tr. 777:7-9.) The molar fraction for tyrosine in a copolymer-1 composition of exactly 6:2:5:1 is

.071. (Sept. Tr. 777:4-6.) Drs. Kent and Grant agreed that, with a fraction of .022 more tyrosine, Mylan's product therefore had 30% more tyrosine. (Sept. Tr. 491:16-492:6 (Gokel); 715:3-8, 777:4-15 (Kent).)

17. Dr. Sampson testified that, while Mylan's proposed product has 9.2% tyrosine (Sept. Tr. 544:11-15), Sandoz's proposed product contains 9.3% tyrosine. (Sept. Tr. 546:21-547:1.) Sandoz's proposed product, with an even greater percentage of tyrosine (9.3%), also contains over 30% more tyrosine than copolymer-1 with a molar ratio of approximately 6:2:5:1.

18. Thus, Teva failed to satisfy its burden to prove that Sandoz's proposed product infringes any of the asserted claims, which all require copolymer 1, defined by the court to be "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively. . . ." (CC Order at 12.)

3. Sandoz's Proposed Glatiramer Acetate Product Has a Weight Average Molecular Weight Greater Than 10 kDa

19. The current process being used to manufacture Sandoz's proposed glatiramer acetate product is called Process 1.1.0. (Sept. Tr. 1094:20-24 (Bishop).)

20. The weight average molecular weight for the most recent lot of glatiramer acetate produced under Process 1.1.0 and reported to the FDA is 10,300 daltons. (PTX-913R at 53.)

21. In an earlier submission to the FDA, Sandoz identified six specific lots of proposed glatiramer acetate. (PTX-349R at SDZ00017953.) The Mw of those six lots were 11,921; 10,993; 11,516; 10,455; 10,469; and 10,517 daltons. (*Id.*)

22. While the record shows that Sandoz may have at one point produced individual lots of glatiramer acetate with a weight average molecular weights of 9966 daltons (PTX 913-R at 53) and 9517 daltons (PTX-349-R at 55), the vast majority of batches produced by Sandoz had weight average molecular weights greater than 10,000 daltons.

23. Teva did not prove by a preponderance of the evidence that the proposed glatiramer acetate product that Sandoz will likely market, if its ANDA is approved, will have a weight average molecular weight less than 10 kDa.

B. Findings of Fact and Conclusions of Law Regarding Claim Construction

1. The Claim Construction Record at Trial

24. Before trial, the Court construed "average molecular weight" to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (CC Order at 40, note omitted.) Since the time of the Court's original claim construction ruling, the Court's understanding of the technology was enhanced by the sixteen days of testimony and argument relating to the subject matter of the patents-in-suit.

25. The Court has revised its claim construction of the "average molecular weight" terms (*e.g.*, "copolymer-1 having a molecular weight;" and "[a] copolymer-1 composition comprising a mixture of polypeptides . . . wherein the mixture has an average molecular weight") to exclude copolymer-1 compositions with a weight average molecular weight of 10 kilodaltons or greater, based on Teva's disclaimer of the copolymer-1 composition in U.S. Patent No. 3,849,550 ("the '550 patent," PTX 26) during prosecution.

26. The '550 patent, PTX 26, claims priority to a patent application filed in April 1971 by Drs. Teitelbaum, Arnon, and Sela – the three Weizmann Institute inventors who are also three of the four named inventors of the patents-in-suit. (PTX 26, '550 patent, col. 1:3-8; PTX 1-9.) The '550 patent cites on its face only one journal article – a publication submitted by Drs. Teitelbaum, Arnon, and Sela to the European Journal of Immunology one month earlier in March 1971. (PTX 26, '550 patent, col. 4:31; PTX 499 at 248.) The 1971 Teitelbaum article expressly identified copolymer-1 and noted that the "average molecular weights of the polymers

were determined, in a Spinco model E ultracentrifuge, from sedimentation and diffusion measurements . . . ." (PTX 499 at 243 § 2.3.1 and Table 1; 244 § 3.7.) No one disputed at trial that the March 1971 article by Drs. Teitelbaum, Arnon, and Sela, describing copolymer-1, described the same work as the '550 patent application filed in April 1971 by the same authors. No one disputed that one of ordinary skill in the art would look to the 1971 Teitelbaum article for additional details not found in the text of the '550 patent. Teva's expert witness, Dr. Gokel, relied on specific examples in the 1971 Teitelbaum article to support his interpretation of the patents-in-suit in forming his infringement opinion. (Sept. Tr. 388:23-391:20.)

27. Sandoz's expert witness, Dr. Scandella testified that one of skill in the art would understand that the reference in the '550 patent to a copolymer-1 with a molecular weight of 10 kDa refers to molecular weight determined by ultracentrifugation based on the related 1971 Teitelbaum article. (Sept. Tr. 1288:9-1290:2.) Dr. Scandella further testified that the particular type of ultracentrifugation described in the 1971 Teitelbaum article (using sedimentation and diffusion measurements from a Spinco model E ultracentrifuge) would provide a weight average molecular weight. (*Id.* at 1290:6:10.) No Teva expert disputed Dr. Scandella's conclusion, and Teva's molecular weight expert, Dr. Gregory Grant, expressly agreed that the 1971 Teitelbaum article obtained its molecular weight values by use of ultracentrifugation. (*Id.* at 1440:3-25.)

28. The trial evidence established that one of skill in the art in 1994 or 1995 (Dr. Scandella) would have understood the average molecular weight determination in the '550 patent to be weight average molecular weight obtained by ultracentrifugation. While there was trial testimony that ultracentrifugation in general could provide both weight average molecular weight and z-average molecular weight (Sept. Tr. 1256:20-23; 1484:19-21), no expert other than Dr. Scandella testified regarding which type of molecular weight would result from the particular

ultracentrifugation specified in the 1971 Teitelbaum article: sedimentation and diffusion measurements from a Spinco model E ultracentrifuge. Thus, Dr. Scandella's testimony that persons of ordinary skill in the art would understand that this form of ultracentrifugation results in weight average molecular weight, and, therefore, would have understood that the '550 patent described weight average molecular weights was undisputed.

29. Dr. Scandella's conclusion was verified by the authors of the 1971 Teitelbaum article and the '550 patent. Dr. Ruth Arnon, an author of the 1971 Teitelbaum paper and an inventor of both the prior art '550 patent and the patents-in-suit, testified that that her team at the Weizmann Institute used ultracentrifugation to obtain molecular weights of copolymer-1. (July Tr. 343:4-344:8.) [redacted]

Dr. Irit Pinchasi, Teva's Copaxone project manager and an originally named inventor of the patents-in-suit, acknowledged that the Weizmann Institute used ultracentrifugation to determine molecular weight of copolymer-1 before Teva later switched to size exclusion chromatography with Superose 12 columns. (PTX 11 at TEV000309434; July Tr. 276:19-277:3.)

2. Teva Disclaimed Copolymer-1 Compositions With a Weight Average Molecular Weight Greater Than 10 kDa During Prosecution of the Patents-in-Suit

30. Throughout the prosecution of the patents-in-suit, both the PTO and Teva addressed rejections over the '550 patent by comparing the molecular weight of the copolymer-1 described in the '550 patent and the molecular weight of the copolymer-1 described in the claims of the patents-in-suit. The PTO relied on the distinction between the '550 patent and the claims of the asserted patents when allowing the patents-in-suit. The PTO's and Teva's distinction

between the molecular weight in the '550 patent and the molecular weight in the patents-in-suit began with the prosecution of the '808 patent. (PTX 1; PTX 13.) Teva sought claims for a copolymer-1 composition with "a molecular weight of about 5 to 9 kilodaltons." (PTX 13 at TEV000304136 (Claim 20).) The Examiner rejected this proposed claim because it was obvious over the '550 patent. (*Id.* at TEV000304142.) The Examiner noted that "[t]he polymers of the prior art ['550 patent] are disclosed to have a specified minimum molecular weight of 10,000. . . ." (*Id.* at TEV000304143, 2/14/97 Office Action at 5.) Teva argued that the Examiner was wrong about the differences between the '550 patent and its invention, specifically arguing that:

> [T]he cited ['550 patent] reference teaches a minimum molecular weight of 10 kilodaltons. In contrast, claim 20 requires a copolymer-1 having a molecular weight of about 5 to 9 kilodaltons. The cited reference does not teach or suggest obtaining the claimed molecular weight fraction of claim 20. . . .

(*Id.* at TEV000304151.) The Examiner accepted this distinction and allowed claim 20 with its "about 5 to 9 kilodalton" limitation. (PTX 13 at TEV000304156 ("The examiner agrees with applicants that the prior art does not fairly suggest, teach, or disclose the subject matter embodies by claim 20.") Claim 20 became claim 1 of the '808 patent. (PTX 1.)

31. Statements by both the Examiner and Teva comparing the '550 patent's teaching of a copolymer-1 with a minimum average molecular weight of 10 kDa to the claimed ranges of the patents-in-suit was not limited to the prosecution of the '808 patent. Other examples are found throughout the prosecution history. (*See* PTX 14 (prosecution history of '808 patent) at TEV000309024; PTX 15 (prosecution history of '898 patent) at TEV000309109 and TEV000309118; PTX 17 (prosecution history of '476 patent) at TEV000304219 and TEV000304384; PTX 18 (prosecution history of '161 patent) at TEV000310336 and

TEV000310449-50; and PTX 19 (prosecution history of '847 patent) at TEV000304449 and TEV000304498.)

32. Teva repeatedly agreed that the '550 patent "teaches a minimum molecular weight of 10 kilodaltons." Teva repeatedly contrasted its proposed claims with the '550 patent based on the distinctions in molecular weight. This constitutes prosecution disclaimer. *See Cordis Corp. v. Boston Sci. Corp.*, No. 2010-1311, -1316, 2011 U.S. App. LEXIS 19738 at *14-*19 (Fed. Cir. Sept. 28, 2011) (affirming trial court's post-trial clarification of claim construction based on arguments made to distinguish prior art); *Day Int'l, Inc. v. Reeves Bros. Inc.*, 260 F.3d 1343, 1349 (Fed. Cir. 2001) (affirming claim construction requiring a lower temperature range based on patentee's comments distinguishing prior art references with higher temperatures); *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324 (Fed. Cir. 2003) ("[W]here the patentee has unequivocally disavowed a certain meaning to obtain his patent, the doctrine of prosecution disclaimer attaches and narrows the ordinary meaning of the claim congruent with the scope of the surrender."); *see also, N. Am. Container, Inc. v. Plastipak Packaging, Inc.*, 415 F.3d 1335, 1345-46 (Fed. Cir. 2005) (holding that patentee disclaimed claim scope based on statements made to distinguish prior art).

C. Conclusions of Law on Non-Infringement

33. Teva's claims under 35 U.S.C. § 271(a) fail as a matter of law because it has not shown that Sandoz's proposed product meets each and every limitation of the asserted claims.

34. An infringement inquiry under 35 U.S.C. § 271(e)(2)(A) requires a comparison of the claims of the asserted patents against the product that is likely to be sold following FDA approval. *See Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002).

35. Momenta's testing of prior batches to determine the proper parameters to carry out its Step 2 reaction cannot be an act of infringement as a matter of law. *See* 35 U.S.C.

§ 271(e)(1) (2006). The Hatch-Waxman safe harbor provisions encourage and permit companies to use patented methods for uses related to submitting information to FDA to support approval of proposed generic drugs. *See, e.g., Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1351 (Fed. Cir. 2004). Therefore, Sandoz and Momenta's early studies on how to carry out the step of reacting protected copolymer-1 with HBr to form TFA cop-1 are protected under the safe harbor provision of 35 U.S.C. § 271(e)(1).

36. As set forth above, after comparing the construed claims to Sandoz's proposed product, Teva has failed to prove that Sandoz's proposed product meets each limitation of the asserted claims of the patents-in-suit.

37. Specifically, Teva did not prove by a preponderance of the evidence that the product likely to be sold by Sandoz, when approved by the FDA, will meet the claim limitation requiring the use of a test reaction to predetermine both time and temperature, as required by Claims 1-3 of the '898 Patent, Claims 1-3 of the '430 Patent, Claim 1 of the '476 Patent, and Claim 1 of the '161 Patent.

38. Teva did not prove by a preponderance of the evidence that the product likely to be sold by Sandoz, when approved, met the "molecular weight" claim limitations because Teva failed to show that Sandoz's proposed product will have a weight average molecular weight of less than 10 kDa, as required by all of the asserted claims.

39. Teva did not prove by a preponderance of the evidence that Sandoz's proposed product met the definition of "copolymer-1" because Teva failed to show that the product is "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine a molar ratio of approximately 6:2:5:1, respectively," as required by all asserted claims.

II. THE ASSERTED CLAIMS ARE INVALID FOR LACK OF ENABLEMENT

A. Findings of Fact on Lack of Enablement

1. Background and Credentials of Sandoz's Experts on Size Exclusion Chromatography and Molecular Weight

40. At trial, Sandoz offered the testimony of Dr. Carl Scandella on the facts underlying Sandoz's lack of enablement and indefiniteness defenses. Dr. Scandella is an expert on size exclusion chromatography ("SEC") and the characterization of molecular weight. (Sept. Tr. 1191:9-15.)

41. Dr. Scandella received a bachelor's degree in chemistry from the California Institute of Technology, and a Ph.D. from Stanford University in biochemistry. (*Id.* at. 1169:21-24, DTX 3564.) Dr. Scandella's Ph.D. research, which included the measurement of molecular weight of protein, was funded by a National Science Foundation Predoctoral Fellowship. (Sept. Tr. 1171:1-6.)

42. During his pre- and postdoctoral work at Stanford, Dr. Scandella worked closely with Nobel Prize winners Roger and Arthur Kornberg. (*Id*. at 1171:1-1172:5.) Dr. Scandella has also studied under and worked with six other Nobel Laureates during his career. (*Id.* at 1189:21-1190:4.)

43. After his post-doctoral work, Dr. Scandella became a professor at State University of New York at Stony Brook, where he taught courses on physical techniques for measuring molecules, including size exclusion chromatography. (*Id*. at 1173:21-23, 1175:8-12.) Dr. Scandella has also taught a course in pharmaceutical biotechnology at the University of Washington for nearly ten years. (*Id.* at 1174:23-1175:4.)

44. Upon leaving Stony Brook in 1981, Dr. Scandella worked for Genex as a principal scientist in protein chemistry, and in 1983, he left Genex for a position with Chiron Corporation. (*Id*. at 1175:13-1176:14.)

45. Dr. Scandella used size exclusion chromatography in every project that he worked on at Chiron. (*Id.* at 1180:4-13.) At Chiron, Dr. Scandella was successful in creating a size exclusion chromatography technique to analyze an antigen that allowed Chiron to develop a Hepatitis-C diagnostic. (*Id.* at 1178:8-1179:6.) This Hepatitis-C diagnostic product, which Chiron later partnered with the Ortho division of Johnson & Johnson to manufacture, resulted in sales in the range of a billion dollars. (*Id.* at 1179:7-14.)

46. While at Chiron, Dr. Scandella was recognized as an expert in SEC by Pharmacia, the manufacturer of the Superose 12 column, and was asked by Pharmacia to serve as a consultant, for which Chiron granted special permission due to the prestigious nature of the assignment. (*Id.* at 1181:14-1183:14.) Dr. Scandella was asked by Pharmacia to use his laboratory as a beta test site for the next-generation Pharmacia SEC column. (*Id.* at 1181:14-24.) As a beta test site, Dr. Scandella's lab was responsible for testing the size exclusion columns from Pharmacia and comparing them to other columns used in the laboratory. (*Id.* at 1181:25-1182:6.) Dr. Scandella was also retained by Pharmacia to develop and teach a laboratory course and lecture for its employees on SEC techniques. (*Id.* at 1181:25-1182:14.)

47. In connection with his work at Chiron, Dr. Scandella developed reference standards that were adopted by the World Health Organization and the National Institutes of Health. (*Id.* at 1185:19-1186:14.)

48. Since 1992, Dr. Scandella has provided consulting services in the areas of biomolecule purification and analysis, process development, and manufacture of clinical lots,

including the use of size exclusion chromatography. (*Id.* 1169:15-18; DTX 3564.) During the course of his career, Dr. Scandella has used a wide variety of analytical techniques for molecular weight measurement, including SEC, ultracentrifugation, MALDI-TOF mass spectrometry, and light scattering, among others. (*Id.* at 1186:17-1187:12.)

49. Dr. Scandella is an inventor on three patents in the field of protein technology. (*Id.* at 1189:10-20; DTX 3564.)

50. At trial, Sandoz offered the testimony of Dr. Randy Wall on the facts underlying Sandoz's lack of enablement and indefiniteness defenses. Dr. Wall is an expert in size exclusion chromatography. (Sept. Tr. 1756:16-20; 1761:18.)

51. Dr. Wall is a Distinguished Professor in the Department of Microbiology, Immunology and Molecular Genetics at the UCLA School of Medicine and is the Associate Director of the UCLA Broad Stem Cell Center. (*Id*. at 1747:15-18.) He has been a professor at UCLA since 1972. (*Id.* at 1747:19-20.) Dr. Wall has a Ph.D. in Microbiology from the Indiana University. (DTX 3562.)

52. Dr. Wall began using size exclusion chromatography for molecular weight determination in graduate school and even made his own SEC beads during that time. (Sept. Tr. 1748:9-22.) As a post-doctoral researcher at Columbia University, Dr. Wall developed a chromatography method that was adopted by Pharmacia. (*Id.* at 1749:23-1750:10.)

53. Since Dr. Wall joined UCLA in 1972, SEC has been "a pretty continuous technique, both for preparative uses and for molecular weight determinations, up at least until the '90s, late '90s" in his laboratory. (*Id.* at 1751:4-16.) Dr. Wall has also supervised the use of SEC as part of his consulting practice in private industry. One of the companies for whom he has consulted is FMC Bioproducts, "a manufacturer and developer of innovative separations and

molecular weight determination materials for columns." (*Id.* at 1752:19-1753:5.) Dr. Wall has supervised "at least 150" researchers on the use of SEC in his laboratory and also teaches a course at UCLA that includes SEC. (*Id.* at 1754:11-1755:6.)

2. What Is Copolymer-1?

54. "Copolymer-l is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath." (PTX 1 at col. 1:10-12.) Copolymer-1 "is a complex substance and it cannot be even called a molecule, because it is actually a mixture of molecules. It's a mixture of copolymer-1 -- of copolymers having the four amino acids in the right molar ratio. But this mixture contains polymers with different sizes." (July Tr. 28:8-13 (Pinchasi).) [redacted]

55. According to Teva, copolymer-1 is also known as glatiramer acetate, which has a brand name of Copaxone. (DTX 1074 at 3 ("COPAXONE® is the brand name for glatiramer acetate (formerly known as copolymer-1)"); DTX 1738 at KRULL0000023 ("Originally known as 'Copolymer-1' or 'Cop-1,' glatiramer acetate was discovered in the 1960s by Israeli scientists at the Weizmann Institute.").) Teva's expert Dr. Grant testified repeatedly at trial that Copaxone is covered by the claims of the asserted copolymer-1 patents. (*See, e.g.*, Sept. Tr. 1471:12-17; 1473:14-18; 1474:24-1475:6; 1475:20-23; 1477:4-9 (Grant).)

56. In a September 2008 submission to the FDA, Teva explained the complexities of copolymer-1 in detail. (DTX 1738.) For example, Teva stated:

> Because the glatiramer acetate in Copaxone® is not a single molecular entity, but rather a heterogenous polypeptide mixture that contains a huge, perhaps incalculable number of active amino acid sequences ('epitopes') in a defined range of molar ratios, FDA has long recognized that 'Copolymer-1 [Copaxone®] is not a conventional drug, either in chemical composition or in its presumed mechanism of action.'"

(*Id.* at KRULL0000024-25; Sept. Tr. 1810:13-1812:13 (Wall).) Teva also stated:

> Given the complexity of the glatiramer acetate in Copaxone®....Teva has spent decades studying the correlations among Copaxone®'s chemical, immunological, and biological properties. These studies have led Teva to design and implement a series of well-controlled manufacturing processes and rigorous testing procedures—developed specifically for glatiramer acetate analysis—to ensure the batch-to-batch consistency, safety, and efficacy of the glatiramer acetate in Copaxone®.

(DTX 1738 at KRULL0000030.) These procedures included the measurement of molecular weight, which is a chemical property of copolymer-1. (Sept. Tr. 1812:9-13; 1813:22-1814:25 (Wall).) Indeed, Teva concluded that "even the most minor changes in the manufacturing of glatiramer acetate - and in the molecular weight distribution of the resulting product - will produce a new molecular entity ('NME') with a significantly different potency and safety and efficacy profile." (DTX 1738 at KRULL0000034.)

3. Molecular Weight of Copolymer-1

57. Due to its complexity, even for those of extraordinary skill in the art, the molecular weight of copolymer-1 must be estimated in the laboratory. (Sept. Tr. 1191:23-1192:9 (Scandella).) It cannot be calculated from the periodic table. (*Id.*) As Dr. Scandella testified, "for a large complicated molecule like cop-1, the meaning of molecular weight becomes fuzzy. One has to specify what method one is going to use to measure molecular weight, because different methods will give you a different answer." (Sept. Tr. 1193:7-10 (Scandella).) Dr. Wall agreed: "For something that's as complicated as copolymer-1 with millions or billions of who knows how many different species, molecular weight becomes much more of an experimental definition and the ways in which you find that molecular weight really depends on the experimental technique that you use." (Sept. Tr. 1762:7-12 (Wall).) Dr. Wall testified that

measuring the molecular weight of copolymer-1 "is a unique challenge. I don't think I've ever heard of a complicated mixture of molecules like this being analyzed before." (Sept. Tr. 1808:10-12 (Wall).) He further testified that copolymer-1 "is an incredibly complicated molecule, probably one of the most complicated mixtures that's ever been analyzed -- certainly that I know of. And it is that immense diversity of molecules and structures and sequences and mixture that in fact confounds the ability of even very sophisticated investigators to arrive at a molecular weight." (Sept. Tr. 1812:17-22 (Wall).)

58. The estimated molecular weight of copolymer-1 "has to be treated as an average molecular weight," because even the smallest sample that can be analyzed contains billions of molecules with different individual molecular weights. (Sept. Tr. 1193:24-1194:11; 1225:18-1226:1 (Scandella).) There is no analytical methodology, today or in 1994, capable of isolating and measuring a single molecule of copolymer-1. (Sept. Tr. 1225:13-17 (Scandella).)

59. There are different types of average molecular weights, including number average ("Mn"), weight average ("Mw"), z-average ("Mz"), and viscosity average ("Mv"). (Sept. Tr. 1195:6-11 (Scandella).) The term "peak average" ("Mp") is also used, but as that term refers to a single point on a molecular weight distribution curve, it is not a true average. (Sept. Tr. 1195:12-19 (Scandella).) For copolymer-1, these average molecular weight values are not the same. (Sept. Tr. 1196:18-23 (Scandella); 1484:22-1485:8 (Grant).) For copolymer-1, the lowest value will be Mn, followed by Mp, Mw and Mz, respectively. (Sept. Tr. 1196:24-1197:7 (Scandella); 1484:22-1485:8 (Grant).)

4. Molecular Weight Disclosure in the Asserted Patents

60. Except for the claims of the '898 patent, each of the asserted claims contains an express numerical limitation on the molecular weight of copolymer-1. (PTX 1-9; Sept. Tr. 1224:16-18 (Scandella); 1764:9-14 (Wall).)

61. The asserted patents are silent regarding how to measure the molecular weight of copolymer-1, except for a single sentence in the specification: "The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12)." (PTX 1, col. 3:6-8.)

62. Gel filtration is another name for size exclusion chromatography. (Sept. Tr. 198:1-3 (Grant).)

5. Size Exclusion Chromatography and the Behavior of Copolymer-1 in Solution

63. SEC can be used to separate a mixture of molecules based on molecular size. (Sept. Tr. 1198:3-20 (Scandella).) It involves the use of a column that is packed with porous beads, such as the Pharmacia Superose 12 column. (*Id.*) The basic principle of SEC is that larger molecules cannot enter the pores of the beads and therefore come out of the column first, while smaller molecules penetrate the pores and trail behind. (*Id.*) The time at which the molecules exit the column is called the retention time. (Sept. Tr. 1199:14-21 (Scandella).)

64. Regardless of one's skill in the art, SEC cannot be used to determine molecular weight directly, because "[b]y itself, a size exclusion chromatography column has no ability to measure molecular weight." (Sept. Tr. 1221:9-10 (Scandella).) Instead, following the SEC run, the molecular weights of the separated material can be estimated with an online detector, such as a light scattering detector, or through the use of a calibration curve. (Sept. Tr. 1211:25-1212:17 (Scandella); DTX 3581 at 7.) A calibration curve is constructed by running standards of known molecular weight through the SEC column and then plotting the retention time on the x-axis versus the log of the molecular weight on the y-axis. (Sept. Tr. 1211:25-1212:17 (Scandella); DTX 3581 at 7.) The molecular weight of an unknown sample can then be estimated by using

the calibration curve to provide a molecular weight for a given retention time. (Sept. Tr. 1212:18-25 (Scandella); DTX 3581 at 7.)

65. Ideally, the standards that are chosen to create the calibration curve will have a similar molecular shape and hydrodynamic volume to that of the unknown sample. (Sept. Tr. 1234:2-9 (Scandella).) That is because molecular shape influences the retention time in an SEC column. (Sept. Tr. 1199:22-25 (Scandella).)

66. Proteins and polypeptides can have a wide range of possible shapes in an SEC column, including "alpha helices, parallel and antiparallel beta pleated sheets, beta helices, etc." (Sept. Tr. 1200:5-10, 1229:16-24 (Scandella).) In an SEC column, it is "difficult to predict what structure [a] polypeptide is going to have at any time." (Sept. Tr. 1200:12-13 (Scandella).) It is "almost certain" that the copolymer-1 molecules in an SEC column will adopt more than a single shape. (Sept. Tr. 1200:14-18 (Scandella).) In 1994, a person of ordinary skill in the art would not have known the shapes that copolymer-1 would assume in solution. (Sept. Tr. 1205:4-8 (Scandella).)

67. The different possible shapes of copolymer-1 in solution are "absolutely critical for the determination of molecular weight by SEC, because the SEC technique is so sensitive to molecular shape." (Sept. Tr. 1204:15-19 (Scandella).) "Because of this shape problem, the molecular weight measured for an unknown sample can be off by tenfold or more if the shape of that sample doesn't agree with the shape of the standards that were used to create the standard curve for the column." (Sept. Tr. 1206:2-6 (Scandella).)

68. Accordingly, the molecular weight results obtained by SEC for a given sample depend on the calibration curve that is used, and SEC molecular weights are therefore relative to

the standards that are chosen. (Sept. Tr. 1213:17-24; 1221:19-25 (Scandella); 1762:25-1763:4; 1765:19-20; 1806:1-4 (Wall); DTX 3581 at 8.) Dr. Grant acknowledged this fact:

> Q. And thus the resulting molecular weight obtained for the sample to be measured when using the SEC method will be reflected by the standards used to calibrate the column, correct?
>
> A. That's correct.

(Sept. Tr. 289:12-16 (Grant).) [redacted]

69. Dr. Scandella made clear at trial that "[t]he SEC technique is not an absolute technique. It never gives an absolute number" for molecular weight. (Sept. Tr. 1205:20-23; 1221:19-25 (Scandella); 1762:25-1763:4 (Wall).) With SEC, "one selects a set of standards and measures the molecular weight relative to those standards and states that the molecular weight is relative to the standards." (Sept. Tr. 1206:6-9 (Scandella).) Dr. Scandella, who was recognized as an SEC expert by the manufacturer of the Superose 12 column, testified that "[w]hatever number you get out of [the SEC] column is relative to how you standardize the column." (Sept. Tr. 1181:14-16; 1221:22-23 (Scandella).)

70. Using SEC, one can obtain values for Mn, Mp, Mw, and Mz. (Sept. Tr. 1197:15-18 (Scandella).)

6. Person of Ordinary Skill in the Art in 1994-95

71. Drs. Scandella and Wall testified that a person of ordinary skill in the art of size exclusion chromatography in 1994-95 would be a person with a Ph.D. in chemistry, biochemistry or a related field, with a minimum of three years of experience in chromatography, or a person who has supervised or directed a research laboratory that conducts chromatography. (Sept. Tr. 1190:15-20 (Scandella), 1756:2-15 (Wall).) Dr. Grant testified that a person of ordinary skill in the art "needs to have an advanced degree or something very equivalent to that in a chemical or biological discipline and they need to have significant experience in the synthesis or characterization of polymers and certainly in the proteins or synthetic peptides" and "access to other scientists who have expertise in those areas." (Sept. Tr. 189:25-190:6 (Grant).)

72. Under either of those definitions, and under any definition, a person of ordinary skill in the art in 1994-95 would have been unable to make copolymer-1 with the claimed molecular weights according to the patents without undue experimentation. (Sept. Tr. 1227:21-1228:11; 1273:13-1274:3 (Scandella), 1825:11-19 (Wall).) That is because the patents do not specify the standards to be used to calibrate the SEC column. (Sept. Tr. 1227:21-1228:11 (Scandella); 1764:18-1765:25 (Wall); Sept. Tr. 330:19-21; 1489:5-7 (Grant).) Although for some molecules of known structure, the details of an SEC analysis can be omitted, that is not the case for large complex molecules such as copolymer-1. (Sept. Tr. 1228:18-1229:2 (Scandella).) No matter one's level of skill in the art, knowledge of the SEC calibration standards used by the inventors is essential to reproduce the claimed molecular weights. (Sept. Tr. 1764:23-1765:25 (Wall).) That is because "the copolymer-1 material is so complicated that it's challenging for any molecular weight measuring technique," and due to the variable and unpredictable molecular

shape in solution, measuring the molecular weight of copolymer-1 by SEC is "clearly not a routine matter." (Sept. Tr. 1229:10-24 (Scandella); *see also id.* at 1766:1-5; 1812:23-1813:7 (Wall).)

7. Teva's 1987-1998 Effort to Determine the Molecular Weight of Copolymer-1

73. From at least 1987 to 1998, Teva scientists and consultants experimented with numerous different analytical methods and different SEC calibration standards to measure the molecular weight of copolymer-1. According to Dr. Scandella, "Teva did what a person of average skill in the art would have done in 1994." (Sept. Tr. 1290:16-20 (Scandella).) Indeed, in this time period, the following scientists were persons of at least ordinary skill in the art under Dr. Scandella's and Dr. Grant's definition of that term:

- Dr. Michael Sela, one of the inventors on the asserted patents, who received a Ph.D. on the synthesis of polytyrosine in 1954, who has been a scientist at Weizmann Institute since that time, and who has significant experience with synthetic polymers, including having written a 200-page book chapter on the subject. (DTX 3569 at 8:19-25; 9:19-21; DTX 1783.) [redacted]
- Dr. Ruth Arnon, one of the inventors on the asserted patents, who received a Ph.D. in biochemistry in 1960 involving the chemical analysis of proteins, and who has been a scientist at Weizmann Institute since the 1960s. (July Tr. 305:3-10; 306:24-307:7.) Dr. Arnon "was the project leader of the whole Copolymer-1 project that was run at the Weizmann Institute" and collaborated with Teva on molecular weight issues. (DTX 3565 at 37:14-39:5.)
- Dr. Irit Pinchasi, who received a Ph.D. in biochemistry in 1984 and began working at Teva in 1986, and who was project manager for the copolymer-1 project for "the next ten years or so." (July Tr. 8:17-24; 10:19-11:12) As project manager, Dr. Pinchasi coordinated all the activities that needed to be done for the copolymer-1 development

project, including "coordinating all the in-house work with the different professional groups, as well as liaising with all the external experts." (*Id.* at 10:21-11:5.)

- Dr. Haim Varkony, who received a Ph.D. in organic and physical chemistry in 1975, who joined Teva in 1979 to lead the analytical development team, and who began working on copolymer-1 in the 1980s. (DTX 4022 at 9:25-10:5; 12:15-18; 15:17-21.)
- Dr. Alexander Gad, who received the equivalent of a Ph.D. and who began working for Teva in 1989 as a senior scientist in Analytical Innovative R&D. (DTX 4016 at 10:19-20; 12:10-17 (Gad).) Dr. Gad's duties in that position included researching analytical methods and characterization, including molecular weight distribution. (*Id.* at 13:6-14:16.) Dr. Gad was involved in creating analytical methods for the molecular weight determination of copolymer-1. (*Id.* at 29:16-24.)

74. Dr. Grant admitted at trial that the scientists at the Weizmann Institute and at Teva have more experience than he does in attempting to measure the molecular weight of copolymer-1. (Sept. Tr. 1478:16-1479:12.) Moreover, Dr. Pinchasi confirmed that the copolymer-1 scientists at Teva had "real expertise" in each aspect of the project:

> Q. You mentioned that there was chemistry work to be done, analytical work. Was the project divided into teams in any way?
>
> A. Yes. We had specific professional teams allocated to each aspect of the project, and these are people who have real expertise in these areas. For example, the chemical team are organic chemists working for years in synthetic chemistry and in scale-up of production, etc. The analytical chemists are people trained to develop methodologies, sophisticated methodologies to analyze molecules different ways, chemical analysis, to develop methodologies and to validate these methodologies....

(July Tr. 15:4-15 (Pinchasi).)

75. Teva's consultants were also persons of ordinary skill in the art in this time period. One of Teva's consultants for the molecular weight determination and other analyses of copolymer-1 was W.R. Grace. (*See, e.g.*, DTX 1762.) "W.R. Grace is a major chemical company. They manufacture a range of bulk chemical products and they also have a contract analytical lab that worked with Teva on this project." (Sept. Tr. 1237:8-10 (Scandella).) Dr. Scandella testified:

> I've read the reports produced by the W. R. Grace laboratory and they appear to me to be well done according to the standards that were in the industry at that time. I have no reason to believe that W. R. Grace is not a reputable contract analytical lab and that the employees are not at least average skill in the art….I've worked with a number of contract analytical labs, and my experience is that the level of skill in the art is high in those laboratories. W.R. Grace is a well-known laboratory.

(Sept. Tr. 1238:10-1239:1 (Scandella).) Thus, the scientists in the contract analytical lab at W.R. Grace were persons of ordinary skill in the art as defined in this case.

76. [redacted] Dr. Krull is a professor in the Chemistry Department at Northeastern University, a position he has held since 1984. (DTX 3568 at 14:13-15:3.) He has a Ph.D. in chemistry and has worked for "many years" in the area of characterizing biopolymers. (*Id.* at 10:8-11; 19:10-16.) Dr. Scandella testified that he took a course from Dr. Krull and that he considers Dr. Krull to be a person of skill in the art. (Sept. Tr. 1340:8-13, 1341:3-5.)

77. A 1987 internal Teva document describes the calibration method that Teva scientists initially tried for measuring the molecular weight of copolymer-1 by SEC. (DTX 3275 at TEV000304991; Sept. Tr. 1230:13-18 (Scandella).) The Teva scientists calibrated the Superose 12 column with commercially available globular protein standards. (DTX 3275 at TEV000304991-92; Sept. Tr. 1230:13-1231:6 (Scandella).) During his testimony in Teva's infringement case, Dr. Grant acknowledged that the scientists at Teva first calibrated the SEC column with globular proteins to measure the molecular weight of copolymer-1. (Sept. Tr. 278:23-279:1; 281:17-24.) Just a few days later, however, during his testimony in Teva's

rebuttal to the defendants' invalidity case, he flip-flopped and denied that Teva ever did so. (Sept. Tr. 1453:20-1454:17; 1495:14-17; 1496:2-5; 1497:2-7.) Only when confronted on cross-examination with the Teva document that plainly states that the first standards used at Teva to calibrate the SEC column were commercially available protein standards, did Dr. Grant flip-flop again and admit that Teva did use globular proteins as standards for molecular weight determination. (Sept. Tr. 1498:1-18.)

78. Using protein standards, Teva found that "[t]he molecular weights of COP-1 batches calculated from the calibration curve of the markers (Fig. 1) were 4-5 times higher than those obtained by viscosity and ultracentrifuge (Table 2)." (DTX 3275 at TEV000304994-95, TEV000304998; Sept. Tr. 1231:16-25 (Scandella).) The markers shown in Figure 1 of the document are commercially available proteins. (Sept. Tr. 1230:23-1231:6 (Scandella).)

79. The asserted patents do not disclose that calibrating an SEC column with commercially available protein standards would yield molecular weight results for copolymer-1 that are four to five times higher than results obtained by other methods. (Sept. Tr. 1232:13-19 (Scandella); 1500:5-12 (Grant).)

80. Calibrating the SEC column with commercially available protein standards would have been a reasonable choice for a person of ordinary skill in the art attempting to measure the molecular weight of copolymer-1 in this timeframe, because proteins "are polypeptides and…there were no other polypeptide molecular weight standards available." (Sept. Tr. 1231:7-13 (Scandella).) Moreover, copolymer-1 was designed to imitate a protein, *i.e.*, myelin basic protein. (July Tr. 18:17-21 (Pinchasi); PTX 1 at col. 1:10-11.)

81. In addition, globular proteins were recommended by the Superose 12 manufacturer, Pharmacia, as the calibration standards for the column. (Sept. Tr. 1231:7-13;

1235:20-1236:17 (Scandella); PTX 752 at TEV000953898.) As Dr. Scandella testified, "[s]ize exclusion chromatography is usually run using protein standards or other commercially available standards. So if I were running a protein or a polypeptide on size exclusion chromatography, I would use the globular protein standards that are recommended by the manufacturer as a starting point." (Sept. Tr. 1229:3-9 (Scandella).) Dr. Wall testified that the Pharmacia literature "was sort of the bible of size exclusion chromatography." (Sept. Tr. 1767:19-24 (Wall).)

82. If one of ordinary skill in the art in 1994 attempted to follow the teaching of the patents and calibrated the SEC column with commercially available proteins, one would not have known that the results obtained were four to five times higher than the results from other methods. (Sept. Tr. 1232:20-1233:1 (Scandella).) Even if one carried out experiments with other methods and discovered that they did not agree with the results using protein standards, one would still not know whether the molecular weights reported in the patents had been measured using protein standards, because "[t]he synthetic procedure for making copolymer-1 gave variable results and it's quite possible that the molecular weight would be different for different lots." (Sept. Tr. 1233:14-19 (Scandella).) As Dr. Pinchasi testified, "you thought you did exactly the same thing each time, but you got molecular weight with very different -- very different molecular weights at the end of the day." (July Tr. 38:21-25.) She further testified that it was "a really tough business" to aim into the "very, very narrow range of molecular weights" that were needed for copolymer-1 to be a pharmaceutical product. (*Id*. at 55:2-6.) Without the benefit of a reference copolymer-1 material for testing and comparison, a benefit that only Teva had in 1994,[1] one of ordinary skill in the art in 1994 would not know whether molecular weights

[1] Copaxone was first offered for sale in the United States in April 1997. (Sept. Tr. 45:17-21 (Congleton).)

obtained with SEC using commercially available proteins were appropriate to compare to the values recited in the asserted claims. (Sept. Tr. 1232:20-1233:1 (Scandella).)

83. Moreover, even if one suspected that copolymer-1 had a different hydrodynamic volume or molecular shape from globular proteins, the proteins could still be appropriate SEC calibration standards, because one could have "simply reported the results as relative to globular protein standards," which is "widely done in size exclusion chromatography." (Sept. Tr. 1235:7-13 (Scandella).) [redacted]

84. In 1987, Teva also began experimenting with the use of copolymer-1 self-standards for SEC column calibration, using molecular weights for the standards that were determined by viscometry. (DTX 3275 at TEV000304999-5000; Sept. Tr. 322:4-323:12 (Grant).) That method is also not disclosed in the asserted patents. (Sept. Tr. 1509:6-9 (Grant); PTX 1.)

85. In a May 4, 1988 document, Teva's consultant W.R. Grace reported the molecular weight results of two copolymer-1 batches, as measured by SEC. (DTX 1762; Sept. Tr. 1236:23-1237:6 (Scandella).) The document was sent to Haim Varkony and Irit Pinchasi at Teva, among others. (DTX 1762 at TEV000360353.) Like Teva, the Grace scientists' first attempt was to calibrate the SEC column with globular protein standards. (DTX 1762 at TEV000360359; Sept. Tr. 1239:3-24 (Scandella); 284:7-11; 1501:22-25 (Grant).) But they too discovered that "[c]alibration with globular protein standards yields calculated molecular weights

for COP-l at least 4-6 times higher than molecular weights determined by viscosity and ultracentrifugation techniques." (DTX 1762 at TEV000360359.) The molecular weight for copolymer-1 batch 13 using SEC calibrated with protein standards was 48,000 daltons. (DTX 1762 at TEV000360361.) Teva had previously obtained a value of 42,000 daltons for batch 13 using SEC calibrated with protein standards and a value of 7,000 daltons using viscosity. (*Id.*) In concluding that the results with protein standards were too high, Grace had the benefit of Teva's viscosity and ultracentrifugation data from their reference copolymer-1 material as a benchmark. (Sept. Tr. 1501:22-1502:11 (Grant).) But those data were not disclosed in the asserted patents, nor were they publicly available in 1994 or 1995. (Sept. Tr. 1499:18-1500:12 (Grant).)

86. The Grace scientists reported to Teva that "appropriate molecular weight standards have not yet been found," and that they had "already begun to work on the use of alternative molecular weight calibration standards for the size exclusion chromatography." (DTX 1762 at TEV000360353, TEV000360359; Sept. Tr. 1239:21-1240:21 (Scandella).) In a section entitled "Suggestions for Future Analytical Studies," the scientists stated that "[a]lternative molecular weight calibration standards (dextrans, polyethylene glycols, polyvinylpyrrolidone, etc.) for size exclusion chromatography can be investigated to obtain accurate COP-l molecular weights." (DTX 1762 at TEV000360370.) These standards were commercially available. (Sept. Tr. 1502:23-1503:4 (Grant).) As Dr. Grant conceded, the Grace scientists did not recommend the use of copolymer-1 self-standards or universal calibration:

> Q. So W.R. Grace tries proteins, they get readings that are too high and they don't say you have to use self standards, right?
>
> A. They don't say that.
>
> Q. They don't say you should use universal calibration, correct?

A. They don't say that.

Q. They say let's try some other commercially available materials to use as standards, right?

A. They say they can be investigated.

(Sept. Tr. 1503:5-14 (Grant); DTX 1762.)

87. In addition to the SEC experiments on copolymer-1, W.R. Grace "investigated cation-exchange chromatography, reverse phase chromatography, proton NMR and fluorine NMR as ways to understand this very complicated molecule." (Sept. Tr. 1241:7-10 (Scandella); DTX 1762 at TEV000360362-69.) As Dr. Scandella explained, "one can't simply do one technique and get a satisfactory answer for a complicated sample like this. [Grace] applied a number of different techniques…to understand the molecule. Some of them give information about molecular weights, but when one's faced with a complicated problem like this, and you want accurate information, you need to use more than one tool to understand it." (Sept. Tr. 1241:10-19 (Scandella).)

88. After the May 1988 study by W.R. Grace, Teva and its consultants continued to work on analyzing the molecular weight of copolymer-1. (Sept. Tr. 1241:20-22 (Scandella).) In a September 9, 1988 document from W.R. Grace to Haim Varkony at Teva, the Grace scientists reported the use of polyethylene glycol (PEG) standards to calibrate the SEC column for copolymer-1 molecular weight analysis. (DTX 1269 at TEV001090148; Sept. Tr. 1248:8-14 (Scandella).) The PEG standards were commercially available. (Sept. Tr. 1504:2-4 (Grant).) Grace analyzed fractions of copolymer-1 batch 13 using an SEC column calibrated with PEG standards and obtained molecular weights ranging from 800 to 11,000 daltons. (DTX 1269 at TEV001090152; Sept. Tr. 1248:19-1249:7 (Scandella).)

89. The results reported in the May 1988 and September 1988 Grace memoranda demonstrate that the molecular weights of copolymer-1 obtained by SEC "depend on which set of standards you use." (Sept. Tr. 1249:23-1250:2 (Scandella).) Both protein standards and PEG standards were appropriate choices that provided appropriate calibrations, yet the results for the same copolymer-1 sample differed by thousands of daltons depending on the calibration used. (Sept. Tr. 1243:20-1244:14; 1250:3-6; 1286:16-1287:9 (Scandella); DTX 1762; DTX 1269; DTX 3538 at TEV000360386.)

90. The September 1988 Grace memo also reported the results of vapor phase osmometry measurements of the molecular weight of copolymer-1, an analysis that Teva had specifically requested that Grace perform. (DTX 1269 at TEV0001090158.) The osmometry result for batch 13 was "Mn=638 daltons, an order of magnitude lower than the expected value of Mn=7,000 reported by TEVA for this COP-1 batch." (*Id.*) Like the choice of SEC calibrated with proteins or PEG standards, Grace's selection of osmometry reflects an appropriate path that one of ordinary skill in the art would have taken to measure the molecular weight of copolymer-1:

> Q. So again they tried a method that they thought was appropriate but when they compared it back to the internal readings from Teva, they realized that that method would not work to measure the standard, right?
>
> A. They realized it wouldn't work.
>
> Q. And again, that information that osmometry is not a good method to use to measure a self-standard to attempt to calibrate a column to measure copolymer-1, that's not disclosed anywhere in any of the asserted patents, right?
>
> A. Doesn't say that osmometry is not a good method.

(Sept. Tr. 1507:17-1508:1 (Grant).)

91. By September 1988, Teva had obtained molecular weight data for copolymer-1 batch 13 using several different methods, including SEC analysis using two different calibration standards. (DTX 3581 at 12; DTX 1269 at TEV001090152, 158; DTX 1762 at TEV000360361; DTX 3059T at TEV000419252; DTX 3538 at TEV000360385; Sept. Tr. 1259:13-1260:11 (Scandella).) The molecular weight values obtained for batch 13 "covered a considerable range," from 638 daltons up to 56,000 daltons, depending on the method or standard chosen. (Sept. Tr. 1259:13-1260:11 (Scandella).)

92. In a March 1992 document, Grace reported the molecular weight results for ten batches of copolymer-1 that Teva used as self-standards. (DTX 1192; Sept. Tr. 1261:8-12 (Scandella).) The molecular weights of the standards were determined by Multiple Angle Laser Light Scattering ("MALLS") and values for Mn, Mw, and Mz were obtained. (*Id.*) For a given sample, there was approximately a two-fold range in molecular weight values between Mn, the lowest value, and Mz, the highest value. (DTX 1192 at TEV001162280; Sept. Tr. 1262:6-24 (Scandella).) Despite the large differences in molecular weight values for the different types of averages, Teva chose the Mn values to define the molecular weights of these copolymer-1 standards and did not use the Mw or Mz values. (DTX 1192 at TEV001162278; Sept. Tr. 1263:5-11 (Scandella); 1493:12-1494:3 (Grant); DTX 4017 at 103:23-104:18 (Gad).) Teva did so solely because the Mn values "would make the best match for the existing fixed calibration curve that was used before." (DTX 4017 at 104:19-25 (Gad).)

93. [redacted]

[redacted]

94. In a November 1992 document, Teva set forth an internal protocol, SI-15247, for the SEC analysis of copolymer-1. (DTX 1701; Sept. Tr. 1264:16-24 (Scandella).) The protocol specified that "[f]or calibration of the Superose 12 columns…COP-1 markers are used. The markers were synthesized by Teva, for this purpose, and their MW was determined by Multiple Angle Laser Light Scattering." (DTX 1701 at TEV001202498; Sept. Tr. 1264:7-12 (Scandella).)

95. The asserted patents do not disclose that copolymer-1 self-standards are to be used to calibrate the SEC column. (Sept. Tr. 1264:12-15 (Scandella); 330:19-21; 1489:12-14 (Grant); PTX 1) The asserted patents do not disclose that if copolymer-1 self-standards are used, their molecular weights should be determined by MALLS. (*Id.*) The asserted patents do not disclose that if copolymer-1 self-standards are used, and their molecular weights are determined by MALLS, that the Mn values should be assigned as the molecular weights of the standards. (*Id.*; 1494:7-9 (Grant).)

96. If a person of ordinary skill in the art decided to use copolymer-1 self-standards and to use MALLS to determine molecular weight of the standards, but did not use the same type of molecular weight average as Teva, *e.g.*, Mn vs. Mw vs. Mz, "they would arrive at a different column calibration, and they would get different results compared to somebody who used the same molecular weight average that Teva used." (Sept. Tr. 1265:21-1266:2 (Scandella).)

97. In a June 1993 document, Grace again reported the Mn, Mw, and Mz molecular weight values for Teva's copolymer-1 self-standards as obtained from MALLS. (DTX 1764; Sept. Tr. 1267:18-23 (Scandella).) At this point in time, the level of effort that Teva had expended to characterize the molecular weight of its copolymer-1 samples and standards was not routine experimentation. (Sept. Tr. 1267:24-1268:4, 1268:10-14 (Scandella).)

98. In August 1995, Teva's consultant Dr. Krull wrote to the Manager of Teva's Analytical R&D Laboratory about the molecular weight of copolymer-1. (DTX 1744.) Dr. Krull stated: "At issue here is the observation that COP-1 results in terms of MW and MW distributions appear to vary from method to method and sample to sample," and that unless certain problems were addressed and overcome, "we can never have comparable results." (*Id.* at TEV001017877-78; Sept. Tr. 1512:13-1513:3 (Grant).)

99. In a September 1995 document, Dr. Haim Varkony of Teva reported the results of a meeting between Teva and the FDA, where "it was agreed to change the method of calibration for molecular weight determination" of copolymer-1. (DTX 1770 at TEV000283327.) The FDA had requested that Teva switch from copolymer-1 self-standards to commercially available standards:

> Presently the calibration methods use copolymer-1 markers and controls which were synthesized by TEVA. These markers and controls have a wide range of molecular weight distribution, and are not commercially available.
>
> The FDA Chemist suggested that we use commercially available proteins or peptides with well defined and narrow molecular weight for calibration. These calibrations can be performed in any analytical laboratory not relying on a single source for markers.

(*Id.*; Sept. Tr. 285:1-6, 285:18-286:6 (Grant).) [redacted]

[redacted]

[redacted]

100. As Dr. Scandella testified, having a single source for self-standards is problematic, because "Teva was the only source for these markers, and they could not easily be reproduced by anyone else." (Sept. Tr. 1275:25-1276:4 (Scandella).) [redacted]

101. In a November 1995 document, Teva recognized this problem: "[c]learly, the use of commercially available standards is desirable." (DTX 3509 at TEV001116158; Sept. Tr. 1276:12-1277:8 (Scandella).) But Teva concluded that "the use of commercially available markers to generate calibration curves that accurately reflect the molecular weight of copolymer-1 is not feasible." (*Id.*)

102. The asserted patents do not disclose that commercially available standards should not be used, and one of ordinary skill in the art in 1994 would not have reached that conclusion upon reading the patents. (Sept. Tr. 1277:9-14 (Scandella); 1500:9-12 (Grant); PTX 1.)

103. In a January 1996 document, Teva listed the commercially available calibration standards that they tried for the molecular weight measurement of copolymer-1 by SEC. (DTX 3510; Sept. Tr. 1277:15-1278:10 (Scandella).) Those standards included polyethylene glycol (PEG), histones, polylysines, globular proteins and denatured proteins. (*Id.*; Sept. Tr. 1511:2-14 (Grant).) After testing these commercially available markers, Teva concluded that "the best

markers" were "copolymer-1 batches with a known molecular weight." (DTX 3510 at TEV001116323.)

104. In an April 1996 document to his Teva colleagues, Haim Varkony wrote: "Attach[ed], please find some questions, suggestions and speculation on MW determination of COPOLYMER-1." (DTX 1706 at TEV001013050.) Dr. Varkony attached a list of 16 "Experimental and conceptual errors in MALLS," directed toward "the problem" Teva was having with MALLS:

> Q. So Dr. Varkony is speculating on what is causing the problem with using MALLS to measure the cop-1 standards, right?
>
> A. He is speculating.

(Sept. Tr. 1520:14-16 (Grant); DTX 1706 at TEV001013051.) MALLS was the analytical method that Teva was using between 1992 and 1998 to measure the molecular weight of its copolymer-1 self-standards and is the method used to create the "calibrated gel filtration column" referenced in the asserted patents. (DTX 1701 at TEV001202498; Sept. Tr. 1521:24-1522:4; 1573:19-22 (Grant); DTX 4016 at 48:14-49:14, 50:20-52:23 (Gad).)

105. The significant differences in molecular weight experienced by Teva were not limited to differences in the type of molecular weight, but included differences in the same type of molecular weight as measured by different techniques. [redacted]

[redacted]

106. In a July 1996 document, Teva recognized that different molecular weight results are obtained for copolymer-1 depending on which method is used, and they set out to correct the problem by trying a mass spectrometry technique:

> The molecular weight for Copolymer-1, which is an heterogeneous mixture of polypeptides, has been determined so far by different techniques, such as analytical ultracentrifugation, SEC chromatography with light scattering detection or with a calibrated SEC column. Depending on the chosen analytical technique, the average molecular weight for Copolymer-1 R.S. 03494 varies between 4700 and 11000 Daltons.
>
> Due to the complex mixture of relatively high molecular weight compounds, a new recently introduced Mass Spectroscopial technique - Matrix Assisted Laser Desorption Ionization with Time of Flight detection [MALDI-ToF] offers the possibility of determining the absolute molecular weight distribution of Copolymer-1.

(DTX 3137 at TEV000290817 (footnotes omitted); Sept. Tr. 1269:13-20 (Scandella).)

107. In this timeframe, mass spectrometry was considered "an appropriate method by which to determine the molecular weight of a polypeptide," and was indeed "becoming a dominant method in this field." (Sept. Tr. 1268:24-1269:3 (Scandella); *see also* 287:2-10 (Grant).) Teva found that "[t]he numeric average molecular weight Mn obtained by the MALDI-ToF experiments is much lower than the value determined by the chromatographic method with MALLS detection (~4000 Da versus ~10,000 Da) or versus ultracentrifugation (~7000 Da)." (DTX 3137 at TEV000290819.) As Dr. Wall explained at trial, "even at this point well into almost a decade of extensive molecular weight characterization, this new method didn't match any of the previous determinations." (Sept. Tr. 1805:5-7 (Wall).)

108. Teva concluded that "[m]olecular weight values for Copolymer-1 R.S. 03494 determined by traditional analytical methods such as light scattering, ultracentrifugation or SEC-chromatography are in the range of 7000 to 11000 Daltons. The differences are due to the experimental bias of the analytical technique and how data are calculated and presented. Therefore, *it should be explicitly stated by which analytical method the molecular weight data were obtained*." (DTX 3137 at TEV000290820 (emphasis added).) Although Teva knew that "[m]olecular weight values for Copolymer-1 determined by MALDI-ToF experiments are considerably lower than those obtained by traditional analytical techniques," Teva did not disclose that information in the patents. (DTX 3137 at TEV290820; Sept. Tr. 1517:13-17 (Grant); 1801:21-1802:1 (Wall).)

109. At trial, Dr. Grant conceded that Teva obtained different molecular weight results depending on the analytical method chosen:

> Q. So you would agree with me that based on the documents as of July of 1996 inside Teva when they used different techniques to measure copolymer-1 they got different molecular weights, correct?
>
> A. If that's what the documents say, that's what they say.
>
> Q. And the recommendation was because of that you need to expressly state what technique is being used, correct?
>
> A. That's what they said.

(Sept. Tr. 291:13-20; *see also* 1516:6-10 (Grant).)

110. Teva's experience supports Dr. Scandella's testimony that copolymer-1 "is an extremely complicated molecule to analyze. When you look at different high, high powered techniques, they don't all give the same answer. So if you want to talk about the molecular weight for cop-1, you need to explicitly state by which method the molecular weight data were obtained." (Sept. Tr. 1271:10-16 (Scandella).) The fact that the patents "explicitly state that you

should use size exclusion chromatography," (Sept. Tr. 326:15-18 (Grant)), does not solve the problem:

> … Q. … Did the disclosure of the asserted patents of the words Superose 12, did that solve this problem identified by Teva?
>
> A. Absolutely not. This in fact is the message I've been saying all day. You need to explicitly state how you determine the molecular weight of your standards in order to understand and know whether you are working within the 5 to 9 range that's specified in the claims of these patents. So this is Teva's own admission that that kind of data is essential in order to know whether you were making and using the material that's described in the claims.

(Sept. Tr. 1826:4-14 (Wall).)

111. [redacted]

112. In 1998, Teva moved away from copolymer-1 self-standards and began using individual synthetic peptide standards for column calibration. (DTX 3507 at TEV000213921; Sept. Tr. 1279:14-24 (Scandella); 1521:21-1522:4 (Grant).) The peptide standards are themselves the subject of several patents, including U.S. Patent No. 7,074,580 ("the '580 patent"), which is assigned to Yeda Research and Development Co., Ltd., one of the plaintiffs in this case. (DTX 3540; Sept. Tr. 1279:25-1280:7 (Scandella).) The lead inventor on the peptide

marker patents is Teva scientist Dr. Gad. (DTX 3539, DTX 3540; DTX 4016 at 12:10-20 (Gad).) The earliest filing date of the peptide marker patents is September 1998. (DTX 3539; DTX 3540; Sept. Tr. 1281:4-8 (Scandella).)

113. According to the '580 patent, as of September 1998, "a need exists for molecular weight markers useful as standards for determining the molecular weight distribution of copolymer compositions contemplated by the invention." (DTX 3540 at col. 3:47-50.) Dr. Scandella agreed with this assessment of the state of the art in 1998:

> Q. Do you agree that in 1998 a need existed for molecular weight marker[s] useful as standards for determining the molecular weight for copolymer-1?
>
> A. Yes, I agree.

(Sept. Tr. 1282:6-9 (Scandella).)

114. According to the '580 patent, calibrating a Superose 12 column with the peptide markers for copolymer-1 molecular weight analysis "has several advantages over the currently used glatiramer acetate molecular weight markers" including "consistency among the various preparations of each batch" and "improved accuracy in molecular weight determination." (DTX 3540 at col. 21:63-22:4.) In its 2008 Citizen Petition, Teva told the FDA that "Teva has developed a unique method of measuring MW distribution based on the separation of glatiramer acetate polypeptides, and calculates the product's MW distribution using a calibration curve generated from a set of well-characterized proprietary polypeptide markers." (DTX 1738 at KRULL0000041; Sept. Tr. 1815:1-1816:4 (Wall).) The asserted patents do not disclose Teva's "unique method of measuring MW distribution," or the use of Teva's "well-characterized proprietary polypeptide markers," which were not even available in 1994. (Sept. Tr. 1816:5-20 (Wall); Sept. Tr. 1281:9-14 (Scandella); Sept. Tr. 1525:6-11 (Grant); PTX 1.) Accordingly, one

of ordinary skill in the art would not have been able to use those markers for column calibration in 1994. (Sept. Tr. 1281:9-14 (Scandella); Sept. Tr. 1816:5-20 (Wall).)

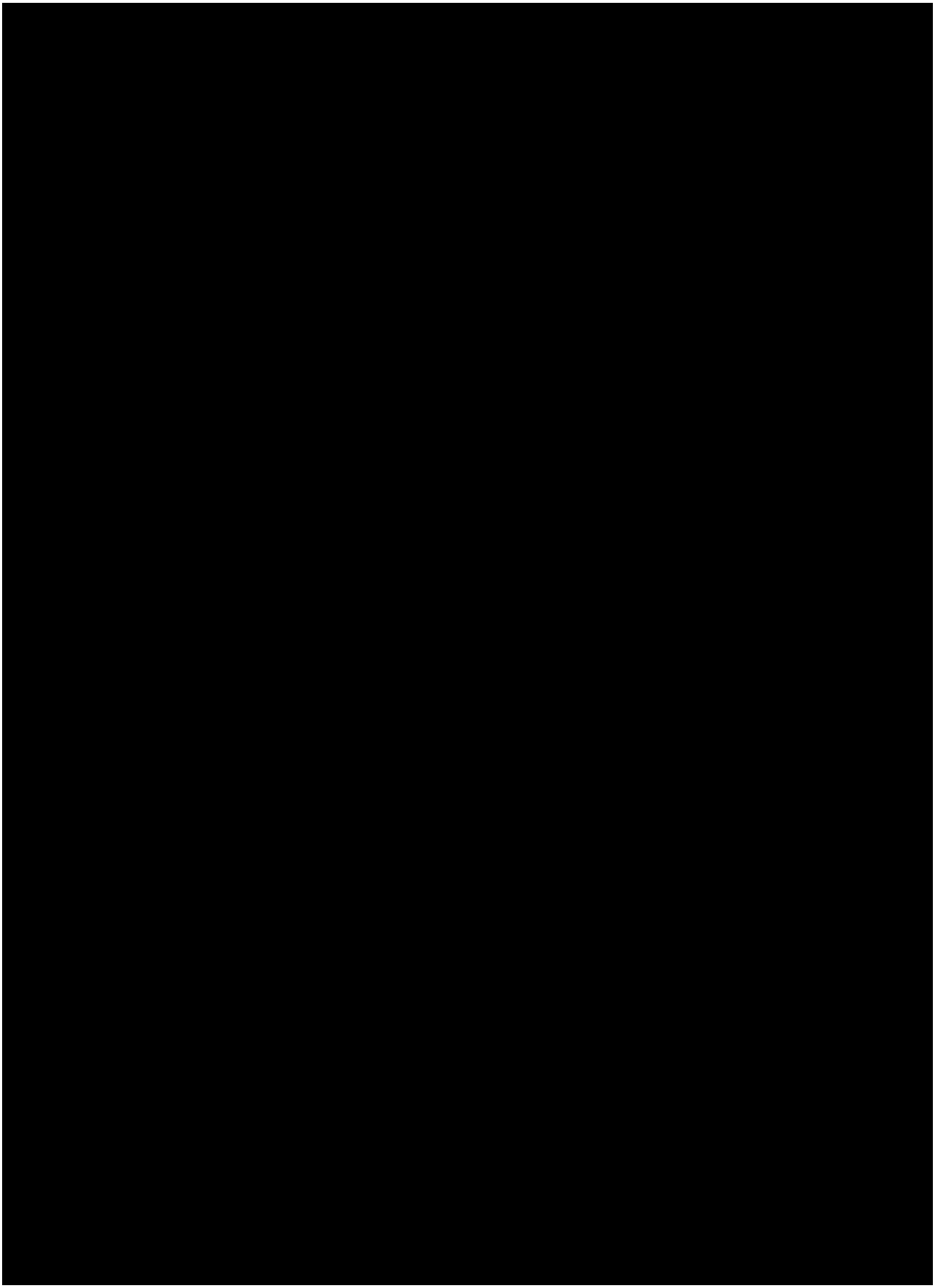
115. Even though Teva knew about the highly variable nature of copolymer-1 molecular weight measurement in 1994 and had been experimenting in this regard for at least seven years, Teva provided no such information in the patents. (Sept. Tr. 1255:2-7 (Scandella).)

> Q. None of this information about the attempts that Teva had made using different and alternative techniques was disclosed in any of the patents, right?
>
> A. That's right.

(Sept. Tr. 1511:15-18 (Grant).)

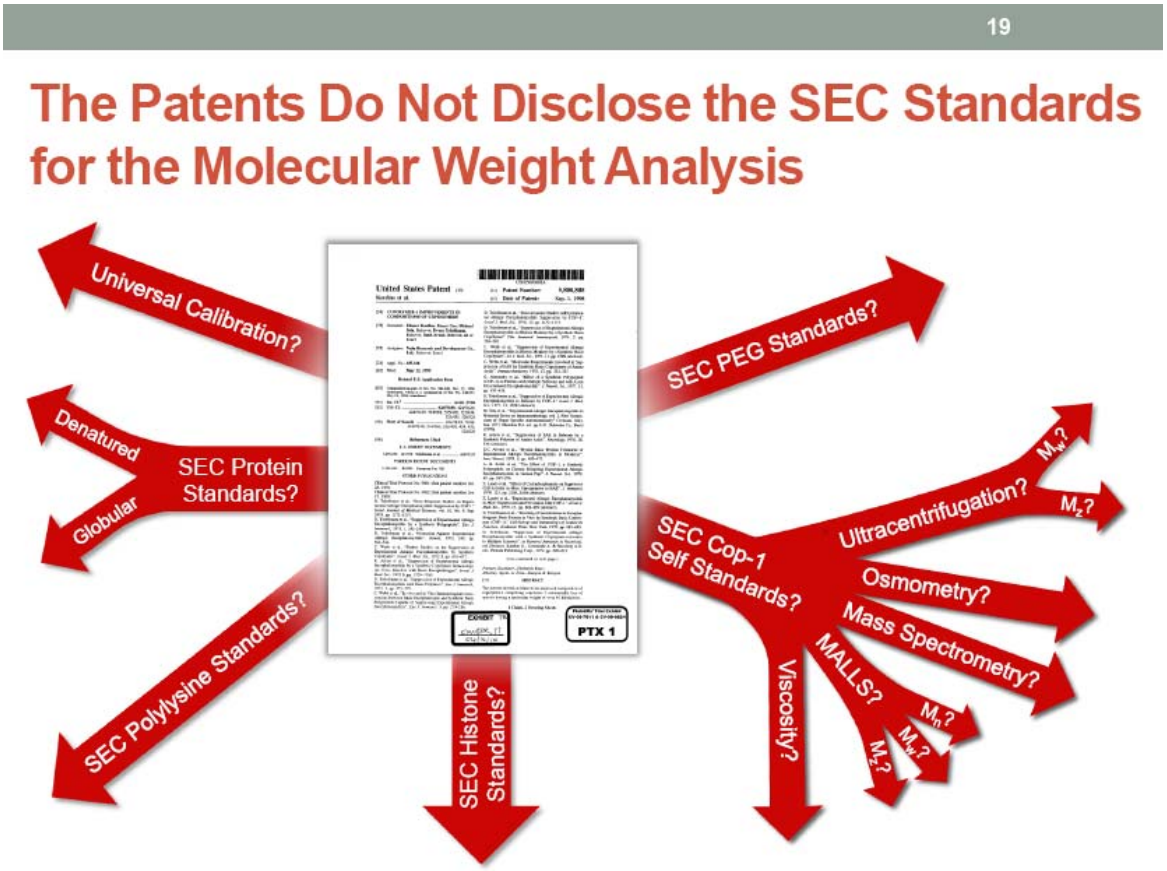
116. Teva's 1987-1998 documentation of its effort to characterize the molecular weight of copolymer-1 is probative of the complexities of copolymer-1 and the disparate molecular weight results one would have obtained in this timeframe, regardless of whether each individual Teva scientist and consultant was a person of ordinary skill in the art as defined in this case. And in any case, Dr. Scandella confirmed that "Teva did what a person of average skill in the art would have done in 1994." (Sept. Tr. 1290:16-20 (Scandella).)

117. Teva had possession of the detailed procedures by which the molecular weight of copolymer-1 should be measured in 1994 but kept that information secret. The following document reveals that the single sentence in the asserted patents on the measurement of molecular weight was part of a larger set of instructions that were deliberately excluded from the patent specification:



[redacted] Teva kept this information secret in order to make generic competition more difficult, using the complexity of copolymer-1 as part of its "strategy" in this regard. (July Tr. 19:23-20:12; 117:22-118:8 (Pinchasi).) [redacted] Dr. Pinchasi testified that copolymer-1 is "absolutely not a simple product or substance to be produced reproducibly. So we felt this by itself is going to constitute a relatively high level of entrance for generic companies, which are usually used to much simpler, very specific chemical entity." (July Tr. 20:6-12 (Pinchasi).)

118. The problem is illustrated by the following slide used by Dr. Scandella at trial:



(DTX 3581 at 19.) As Dr. Scandella explained, this slide shows:

> the different approaches that one of skill in the art would have taken, and some branch points in these approaches in leading to a calibration method for giving the molecular weight of copolymer-1 by size exclusion chromatography....[T]his figure illustrates the complex problem that Teva faced when they invented cop-1, and it's the same problem that one of skill in the art would have faced in 1994....So this is a tough problem, and in my opinion it's way beyond what one could call ordinary experimentation.

(Sept. Tr. 1293:15-21 (Scandella).) The pathway that Teva had chosen by 1994, *i.e.*, copolymer-1 self-standards, analyzed by MALLS, and the assignment of number average molecular weight, was not disclosed in the patents. (Sept. Tr. 1264:12-15 (Scandella); DTX 3581 at 20; 330:19-21; 1489:20-25; 1494:7-9 (Grant); 1801:21-1802:1 (Wall); PTX 1.) As Dr. Wall explained at trial, that pathway was the product of years of experimentation: "we certainly

are looking at a very concerted, very high activity, very expensive and long-term effort by Teva and some of their outside contractors to establish a standard way to determine molecular weight." (Sept. Tr. 1807:6-9 (Wall).) One of ordinary skill in the art "might well make a different choice and if they made a different choice they would arrive at a set of standards that would yield different molecular weight values than the ones that Teva did." (Sept. Tr. 1295:10-13 (Scandella).)

119. [redacted]

[redacted]

120. As a result, for one of ordinary skill in the art in 1994 "it would have taken an extraordinary amount of effort to find a way to standardize, to calibrate the SEC column and once one had done that it wouldn't necessarily be the same molecular weight, yield the same molecular weight values as Teva's values." (Sept. Tr. 1290:16-1291:1, 1291:9-17 (Scandella).)

121. [redacted] As Dr. Scandella testified at trial, there is no analytical methodology, today or in 1994, capable of isolating and measuring a single molecule of copolymer-1. (Sept. Tr. 1225:13-17 (Scandella).)

8. The Use of Self-Standards Would Not Have Enabled the Claims

122. Dr. Scandella, who has created self-standards that have been adopted by the World Health Organization and the National Institutes of Health, testified that "[t]he task of

creating standards that match a sample as complicated as cop-1 is quite difficult and may take years." (Sept. Tr. 1206:9-11; 1250:7-1251:12 (Scandella).) He characterized it as a "major research project" and "major undertaking" that would not "yield a single well-defined product." (Sept. Tr. 1251:13-22; 1252:7-9 (Scandella).) Dr. Scandella further testified about the inherent variability of any copolymer-1 self-standards:

> Q. In your opinion, would batch-to-batch consistency have been an issue for one of skill in the art trying to use copolymer-1 self standards?
>
> A. Yes, I believe it would have.
>
> Q. Why?
>
> A. Because the synthetic procedure for making cop-1 had an inherent variability, so it was not possible to make two batches that were identical. So this means that this would be a problem for the synthesis of cop-1 markers.

(Sept. Tr. 1283:3-11 (Scandella).) [redacted]

123. And even if one made a copolymer-1 self-standard, "there was no good way to measure the molecular weight of a cop-1 standard in 1994." (Sept. Tr. 1251:25-1252:1 (Scandella).) Dr. Wall agreed:

> Q. So let me turn to that. Given that the patents don't mention the use of self standards, in your opinion would the use of self standards have been a reasonable choice for someone with skill in the art in 1994 and 1995 to attempt to measure the molecular weight of copolymer-1?
>
> A. I don't think so. First of all, it's not certain that they would be able to obtain self standards such as Teva had and also made and, secondly, it's not clear they would be able to make self standards and then they still would have been faced with the insurmountable problem in terms of setting up the molecular weight calibration of determining the molecular

weight method that would be used to characterize your standards.

(Sept. Tr. 1819:21-1820:8 (Wall).)

124. Dr. Grant acknowledged that the molecular weight of an SEC standard must be determined by some other method:

> Q. Doctor, as you testified yesterday, even after you select what type of standard to use, you then must use another method or technique to determine the molecular weight of the standard, correct?
>
> A. Yes.
>
> Q. In other words, before you can calibrate an SEC column using a known standard you have to know the molecular weight of the standard, right?
>
> A. They have to be determined, yes.

(Sept. Tr. 286:22-287:5 (Grant).) And, "[a]s Teva showed, you need to use many different methods and make choices about which method and which type of molecular weight average to use," because the measured molecular weight of copolymer-1 varies depending on the method that is used. (Sept. Tr. 1252:1-3; 1254:1-3 (Scandella).) Dr. Grant agreed:

> Q. But depending on the method used to measure the molecular weight of the self-standard you may get a different type of molecular weight, right?
>
> A. You may.

(Sept. Tr. 1487:21-24 (Grant).) Dr. Pinchasi also agreed:

> Q. Now you understand that a material that would be measured at 14,000 kilodaltons with one method can be about 11,000 with another method; correct?
>
> A. I understood from analytical chemists, although I'm not a chemist and I cannot explain why is this, that different methods can provide different results.
>
> Q. And it was your understanding at the time that it's not easy to compare side by side data from different methodologies, correct?
>
> A. It's not easy. You have to understand very well what you are

measuring.

(July Tr. 277:13-23 (Pinchasi); *see also id.* at 254:23-25.) Dr. Pinchasi further testified that "there was no way to really control the molecular weight of the final [copolymer-1] product. You did -- you thought you did exactly the same thing each time, but you got molecular weight with very different -- very different molecular weights at the end of the day." (July Tr. 38:21-25 (Pinchasi).)

125. Teva tried a variety of analytical techniques to measure the molecular weight of copolymer-1, including mass spectrometry, ultracentrifugation, viscosity, osmometry and MALLS. (Sept. Tr. 1253:14-25 (Scandella).) Although certain of these methods, such as mass spectrometry, osmometry, ultracentrifugation, and light scattering, are considered to provide absolute molecular weights, "that doesn't mean that every measurement by all of these techniques gives you an absolute molecular weight. All of these methods are subject to limitations and complication, especially when dealing with complex molecules….[l]ike copolymer-1." (Sept. Tr. 1207:21-1208:7 (Scandella); 1763:5-15 (Wall).) "[T]here is no assurance that any one technique is going to give absolute values for the cop-1 molecular weight." (Sept. Tr. 1261:21-22 (Scandella).) [redacted] Thus, even after the asserted patents were filed, determining the absolute molecular weight of copolymer-1 was "still just a possibility," and "none of the measurements done so far had yielded an absolute measure of molecular weight" of copolymer-1. (Sept. Tr. 1269:21-24 (Scandella); 1802:14-18 (Wall).)

126. Moreover, these analytical methods "don't all yield the same type of average molecular weight." (Sept. Tr. 1254:4-7 (Scandella).) A viscosity measurement yields viscosity

average molecular weight. (Sept. Tr. 1256:16-19 (Scandella).) Ultracentrifugation yields z-average or weight average molecular weight. (Sept. Tr. 1256:20-23 (Scandella).) Osmometry yields number average molecular weight. (DTX 1269 at TEV00010901158.) MALLS yields number average, weight average and z-average molecular weight. (DTX 1764.) A mass spectrometry measurement, such as MALDI-ToF, can yield number average molecular weight. (DTX 3137 at TEV000290819.)

127. Several documents introduced at trial show the wide range of molecular weight results that Teva obtained for its copolymer-1 self-standards, depending on the method chosen. For example, a table in a November 1995 document lists 15 copolymer-1 markers and their average molecular weights obtained by ultracentrifugation, viscometry and MALLS. (DTX 3509 at TEV001116167; Sept. Tr. 292:6-23 (Grant).) Depending on the method that was used, the molecular weight for a given standard varied by up to 2,100 daltons (marker 02095 [5,800 - 7,900 daltons]) in the lower end of the molecular weight range and up to 3,000 daltons in the upper end of the range (marker BD-402 [22,200-25,200 daltons]). (DTX 3509 at TEV001116167.)

128. Additional molecular weight data for these same markers confirms the problem. An August 1995 document lists the Mw and Mn MALLS results for these same 15 markers, and another document lists additional Mw and Mn results from several other molecular weight analyses on these same markers. (DTX 1699; Sept. Tr. 1527:4-1528:19 (Grant); DTX 1642 at TEV001013041, TEV001013087; Sept. Tr. 1528:23-1529:24 (Grant).) When all of these data are considered, even greater variation is revealed in the estimated molecular weight of a given copolymer-1 marker. For marker 02095, for example, there was a variation of nearly 5,000 daltons for the Mn values (5,200 - 10,100 daltons) and a variation of 9,000 daltons for the Mw

values (5,800 - 14,800 daltons). (DTX 1699 at TEV000950015; DTX 1642 at TEV001013041.) The variation was even more pronounced for higher molecular weight markers. The Mw value of marker BD-402, for example, varied from 22,200 to 48,900 daltons depending on the analysis selected. (*Id.*)

129. It is clear from these data that Teva obtained highly variable results for the molecular weight of copolymer-1 standards even among methods that yield the same type of molecular weight average. (*See* DTX 1269 at TEV00010901158; DTX 3137 at TEV000290819.) That is because "for a large complicated protein-like problem like this, there is no, there is no set solution." (Sept. Tr. 1254:16-17 (Scandella).) Accordingly, calibrating an SEC column with copolymer-1 self-standards would lead to different molecular weights depending on how the molecular weights of the self-standards were measured. (Sept. Tr. 1272:5-10 (Scandella); 1803:7-14 (Wall); DTX 3581 at 16.) The osmometry result obtained for batch 13 in 1988, for example, was 638 daltons, an order of magnitude lower than the expected value of 7,000 daltons. (DTX 1269 at TEV0001090158.) In that timeframe, osmometry was considered an appropriate method by which to determine the absolute molecular weight of a polymer. (Sept. Tr. 1258:22-25 (Scandella).) If a person of ordinary skill in the art had made copolymer-1 self-standards and characterized their molecular weights by osmometry, "their values would be about ten fold too low." (Sept. Tr. 1259:1-6 (Scandella).) One would not know that the molecular weights of the self-standards were off by a factor of ten "without doing other experiments." (Sept. Tr. 1259:7-9 (Scandella).) As Dr. Scandella testified, the selection and use of self-standards would have required extensive experimentation:

> Q. In your opinion, if one of skill in the art in 1994 had decided to use self standards, do the patents provide sufficient information to enable them to make or to know they have made the same copolymer-1, without undue experimentation?

> A. The patents are silent on this purpose -- on this point. They don't even state that self standards were used.
>
> Q. And in your opinion, could a person of ordinary skill in the art in 1994 have figured that out without undue experimentation?
>
> A. In my opinion, it would be a very large amount of experimentation comparable to what Teva did.

(Sept. Tr. 1273:13-23 (Scandella).)

130. Dr. Wall explained the problem with self-standards as follows:

> [W]hen you use even absolute molecular weight determinations on the same copolymer-1 batch, you get a range of values from 4,000 to 11,000. So any one of those absolute molecular weight determinations could be used to calibrate your standards and determine their molecular weight. That being the case, a person of ordinary skill would not know unless you told them in the patent how the molecular weights had been determined and what the standards were like. So essentially, he would be in the dark.

(Sept. Tr. 1818:18-1819:1 (Wall).) As a result, "[y]ou'd get a very different calibration curve."

(Sept. Tr. 1819:2-14 (Wall).)

131. [redacted] Teva itself had reached the same conclusion in 1995, observing that for SEC, "the sample molecular weight distribution and the calculated molecular weight averages are at best an approximation relative to the standard used. Copolymer-1 markers having the same structure and conformation have been prepared and

are employed for estimation of molecular weights." (DTX 3509 at TEV001116165.) Teva even changed its molecular weight specifications because of this issue: "The term determination with respect to molecular weight was changed to estimation, *in response to FDA's expressed doubts about the accuracy furnished by a calibration based on glatiramer acetate markers*." (DTX 3507 at TEV000213922 (emphasis added); Sept. Tr. 1523:14-1524:2 (Grant).)

132. In 1998, Teva informed the FDA that the difference in copolymer-1 molecular weight values calculated from the peptide markers versus the self-standards was as high as 20 percent:

> The calibration based on the new polypeptides was compared to the currently used calibration based on glatiramer acetate molecular weight markers (Table 3b). The molecular weights obtained using the two calibration sets within the specification range differed by, typically, not more than 20%, in the low molecular weight range and by not more than 12% in the RRT specification range of the peak (average molecular weight).

(DTX 3507 at TEV000213933.)

133. Dr. Scandella concluded that if copolymer-1 self-standards were the intended calibration method of the asserted patents, additional information should have been included in the patents about the self-standards. (Sept. Tr. 1253:1-13 (Scandella).) That information includes "detailed conditions of how they were synthesized and purified…how they were characterized and what method and what type of molecular weight average and so forth was used," all of which is "information that one would need in order to reproduce this material." (Sept. Tr. 1253:4-12 (Scandella).)

134. Accordingly, it would have required undue experimentation for a person of ordinary skill in the art to make copolymer-1 with the claimed molecular weights using self-standards on the effective filing dates of the asserted patents.

9. The Use of Universal Calibration Would Not Have Enabled the Claims

135. Universal calibration was not a common and widespread technique in the field of biotechnology and pharmaceutical products in 1994 or 1995. (Sept. Tr. 1284:13-18 (Scandella).)

136. Universal calibration is based on a fundamental assumption that separation in an SEC column, and thus the retention time, is based only on molecular size. (PTX 514 at 213; Sept. Tr. 1423:19-1424:22 (Grant).) Dr. Grant acknowledged this assumption at trial:

> Q. Dr. Grant could you explain what's provided in this section of Plaintiff's Trial Exhibit 514?
>
> A. This section essentially is talking about the various different derivations from different laboratories that have been presented in the literature, that underpins the basis for universal calibration. But they all end up using some property like viscosity.
>
> [….]
>
> Q. Yes, if you could read the first sentence of the first paragraph, please.
>
> A. "If well characterized fractions of the polymer under test are not available and the effort required to prepare them is not worthwhile, then a calibration curve can be obtained by making some assumption about the mechanism of GPC separation."
>
> Q. What is the assumption about the mechanism of GPC separation that's referred to in that sentence?
>
> A. I believe that the assumption that they're referring to here is that molecules of the same size come out of the column at the same time.

(Sept. Tr. 1423:25-1424:22 (Grant).)

137. Factors other than size, however, can influence the retention time, including "interaction between the column matrix and the sample, for example, ion exchange interactions." (Sept. Tr. 1200:1-4 (Scandella).) Universal calibration does not account for these interactions. (*See* PTX 514 at 216 ("The [universal calibration] method depends upon separation being size

dominated and will break down if adsorption of polymer is significant").) Moreover, according to the authors of a 1989 article in the journal Analytical Biochemistry ("1989 Le Maire article"), "the concept of universal calibration requires several qualifications and can be used only as an approximation in most cases." (DTX 3353 at 51; Sept. Tr. 1287:14-1288:1.)

138. Teva and its consultant W. R. Grace were aware of the possibility of using universal calibration for the molecular weight determination of copolymer-1 at least as early as May 1988. (DTX 3538 at TEV000360384; Sept. Tr. 1285:13-1286:12 (Scandella).) Despite being aware of universal calibration, there is no evidence in the record that Teva or any of its consultants ever used, or even tried using, universal calibration for the molecular weight determination of copolymer-1. (Sept. Tr. 1285:5-8 (Scandella); 1535:4-7 (Grant).)

139. There is no mention of universal calibration in the asserted patents. (Sept. Tr. 1286:13-15; (Scandella); 1534:25-1535:3 (Grant); PTX 1.)

140. The universal calibration literature on which Dr. Grant relied at trial states that universal calibration equations apply to "any flexibly coiled molecule." (PTX 514 at 213; Sept. Tr. 1425:1-6 (Grant).) Dr. Grant testified that a flexibly coiled molecule is the same as a random coil. (Sept. Tr. 1425:7-23 (Grant).) Teva's measurements from 1993 demonstrate that copolymer-1 has secondary structure and is not a random coil. (DTX 1113 at TEV000312034.) In particular, Teva's results show that "[r]elatively high α-helical conformation (secondary structure) of COP-l was determined by circular dichroism and confirmed by FT-IR. A non-random distribution of helicity was found …. [I]n spite of a random synthesis, COP-l is, essentially, a mixture of polypeptides having a non-random primary structure of a certain α-helix secondary structure." (DTX 1113 at TEV000312034; Sept. Tr. 1202:11-1204:4 (Scandella).)

141. Even if copolymer-1 were random coil, universal calibration would still be problematic, because in the 1989 Le Maire article, the authors conclude that "the inherent ambiguity in defining the molecular radius of macromolecules such as random coils and long rods, which in their conformation deviate very much from a compact, spherical shape, represents an obstacle to universal calibration of gel columns." (DTX 3353 at 55.)

142. Accordingly, it would have required undue experimentation for a person of ordinary skill in the art to make copolymer-1 with the claimed molecular weights using universal calibration on the effective filing dates of the asserted patents.

10. Momenta's Effort to Determine the Molecular Weight of Copolymer-1

143. A document dated February 2008 reports on the attempts of Momenta scientists to reproduce the copolymer-1 of the asserted patents. (PTX 236; Sept. Tr. 1245:1-6 (Scandella).) According to the document, "[a] variety of conventional protein standards were initially used to generate a calibration curve. This approach is easy to implement as the proteins are commercially available. It is also the approach disclosed in US Patent 6,939,539 B2 (listed in the Orange Book for Copaxone®) to characterize molar mass of Glatiramer Acetate." (PTX 236 at MMT00638170; Sept. Tr. 1243:4-13 (Scandella).) Molar mass is another term for molecular weight. (Sept. Tr. 1243:15-16 (Scandella).) U.S. Patent 6,939,539 B2 is one of the patents asserted in this case. (PTX 8.)

144. Momenta scientists further reported that "[a]n effort was made to reproduce as close as possible the innovator method, with the amount of information available in the literature. No development was performed on the chromatographic conditions. The column used was a Superose 12 10/300 GL from GE Healthcare, and the column was calibrated with the exact calibration kit recommended by the manufacturer of the column." (PTX 236 at

MMT000638173; Sept. Tr. 1244:17-1245:6 (Scandella).) The phrase "reproduce as close as possible the innovator method" means to reproduce what is in the '539 patent. (Sept. Tr. 1245:1-6 (Scandella).) The phrase "exact calibration kit recommended by the manufacturer of the column" refers to "a set of globular proteins." (Sept. Tr. 1245:7-10 (Scandella).)

145. Upon reading the '539 patent, selection of protein standards would be a reasonable choice for SEC column calibration, and Momenta's approach to SEC calibration for copolymer-1 was the same approach that one of ordinary skill in the art would have taken in 1994. (Sept. Tr. 1243:20-25; 1245:11-14 (Scandella).)

146. Although the use of protein standards would yield higher molecular weight results for copolymer-1 compared to other calibration standards, the use of protein standards would have provided "'relative molar mass results'" and would have been an appropriate calibration for the reasons stated above. (PTX 236 at MMT00638170; Sept. Tr. 1244:1-11 (Scandella).) Protein standards would not have been an "inappropriate choice." (Sept. Tr. 1244:1-14 (Scandella).)

147. Momenta ultimately developed a method for determination of the molecular weight of copolymer-1 using the "reference listed drug," *i.e.*, Copaxone, as the starting point and "after considerable work." (Sept. Tr. 1314:5-14 (Scandella).) Dr. Scandella testified about the significance of having the reference listed drug available to define the molecular weight target:

> Q. What is the significance of having that [reference listed drug]?
>
> A. Well, the reference listed drug is a standard for you. You know the molecular weight data for that standard from the reference listed drug information, and you can use that information to calibrate your method.
>
> Momenta scientists have indicated it would have been very difficult to develop that method without that reference material.

(Sept. Tr. 1336:1-8 (Scandella).) Indeed, former Momenta scientist Dr. Corrine Bauer testified that with respect to the molecular weight determination of copolymer-1, "[t]he first product we

analyzed was a reference listed drug." (PTX 956 at 43:6-7.)

148. Momenta scientists also had the peptide standards from the Gad patents and "were able to use the approach used in the Gad patents to create their own peptide standards. That material, that information would not have been available, of course, in 1994 or 1995." (Sept. Tr. 1336:9-15 (Scandella).) Dr. Bauer confirmed the importance of the Gad patents in this regard:

> Q. Now, when you started working on the accurate method of determining the molecular weight, what technique did you use?
>
> A. We evaluated a lot of things. We really tried to understand what the innovator was doing. And it's not before the Gad patents that we got some light on how the molecular weight -- what type of molecular weight, you know, the label -- the label was referring to and how it was -- this result was obtained.

(PTX 956 at 55:13-24.)

B. Conclusions of Law on Lack of Enablement

149. Section 112 of the Patent Act requires that a patent specification include "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112, ¶ 1.

150. Whether a patent disclosure is enabling is an issue of law based on underlying factual inquiries. *Enzo Biochem, Inc. v. Calgene, Inc*., 188 F.3d 1362, 1369 (Fed. Cir. 1999). Enablement is determined as of the effective filing date of the patent's application. *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010). Courts may, however, use later references "as evidence of the state of art *existing on the filing date* of an application." *In re Hogan*, 559 F. 2d 595, 605 (C.C.P.A. 1977) (emphasis in original); *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1343-44 (Fed. Cir. 2003) ("Report of a first success after

1987 indicates failure or difficulty in or before 1987."). "[L]ack of enablement must be proven by clear and convincing evidence." *ALZA*, 603 F.3d 940.

151. "[A] specification need not disclose what is well known in the art. However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) (internal citation omitted). In other words, Teva "cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification." *ALZA*, 603 F.3d at 941. As the *Genentech* court explained, "omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art." *Genentech*, 108 F.3d at 1366.

152. The absence in the specification of any information on the SEC calibration standards to be used for the molecular weight analysis of copolymer-1, and the absence of the method by which the molecular weights of any self-standards are to be measured, are not "minor details." *Id*. That information is the "specific starting material" necessary to practice the claimed invention, and without it, undue experimentation is required. *Id.* (Sept. Tr. 1227:21-1228:8; 1273:13-1274:3 (Scandella), 1764:18-1765:25; 1825:11-19 (Wall).) Dr. Grant's testimony that one of ordinary skill in the art would know how to calibrate the SEC column to practice the claimed invention based on the one-sentence disclosure in the patents, (Sept. Tr. 1397:20-1398:1), is nothing more than a bare assertion that "all the disclosure related to the

process is within the skill of the art," an approach that the Federal Circuit has specifically rejected. *Genentech*, 108 F.3d at 1366.

153. "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." *Id.* "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Id.* at 1365 (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)); *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1378 (Fed. Cir. 2007). Some experimentation is permissible, provided it is "routine," and not "undue." *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988).

154. The Federal Circuit in *In re Wands* set forth a number of factors to consider in determining whether a disclosure would require undue experimentation, including:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Id. at 737; *see also Enzo*, 188 F.3d at 1371-75. "[I]t is not necessary that a court review all the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory. What is relevant depends on the facts." *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). A court may rely on expert testimony to determine whether undue experimentation is required to practice a claimed invention. *Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1284 (Fed. Cir. 2007).

155. Here, application of each of the *Wands* factors compels the conclusion that the one-sentence disclosure on molecular weight determination in the asserted patents is not enabling.

Factors # 1 (Quantity of Experimentation) and # 6 (Skill in the Art)

156. No amount of experimentation or level of skill would remedy Teva's inadequate disclosure of molecular weight methodology, because the patents do not even teach the starting point, *i.e.*, the SEC calibration standards and how to measure the molecular weight of those standards. (Sept. Tr. 1227:21-1228:11 (Scandella); 1764:18-1765:25 (Wall).) Persons skilled in the art are left to choose from a variety of commercial standards, or develop their own set of standards and choose one of many methods to obtain the necessary, independent molecular weight values for those self-standards. (DTX 3581 at 19; Sept. Tr. 1293:15-1295:1.) Such experimentation may have taken "several years" and would have been far from routine. (Sept. Tr. 1227:21-1228:11; 1291:18-25 (Scandella).) That fact alone warrants a finding of undue experimentation. *See, e.g., White Consol. Industries, Inc. v. Vega Servo-Control, Inc*., 713 F.2d 788, 791 (Fed. Cir. 1983) (18 months to two years of effort is undue experimentation); *In re Ghiron*, 442 F.2d 985, 992 (C.C.P.A. 1971) (period of "many months or years...does not bespeak of a routine operation but of extensive experimentation and development work"). But even at the end of that process, the molecular weight results for the copolymer-1 self-standards would vary widely, depending on the method chosen, confounding any attempt to reproduce the claimed invention. (*E.g.*, DTX 3137 at TEV000290819.)

157. Because molecular weight results obtained by SEC are always relative to the standards used, one would have no assurance that the molecular weight values obtained for a set of copolymer-1 samples could be compared to those claimed in the patents, which are based on unknown standards. (Sept. Tr. 1213:17-24; 1221:19-25 (Scandella); 1825:5-19 (Wall).) For this reason, the patent does not teach how to make "the same" copolymer-1 described and claimed in

the patents, as required by 35 U.S.C. § 112. The copolymer-1 scientists recognized the importance of using the same molecular weight procedures:

> Q. So if you want to -- if you want a reproducible procedure for determining the molecular weight, you need to use the same markers each time?
>
> A. This is what makes sense. And I don't know what was done here.

(DTX 3565 at 164:10-15 (Arnon).)

> Q. And was it important to you as the overall project manager of copolymer-1 at the Weizmann Institute that the molecular weight be determined exactly the same way so that one batch could be compared to the other batch as for the molecular weight size?
>
> A. It was important.

(July Tr. 343:24-344:4 (Arnon).) [redacted] In its Citizen Petition, Teva explained why using exactly the same process is so essential: "[E]ven the most minor changes in the manufacturing of glatiramer acetate-and in the molecular weight distribution of the resulting product-will produce a new molecular entity ('NME') with a significantly different potency and safety and efficacy profile." (DTX 1738 at KRULL0000034.)

Factors # 2 (Amount of Direction or Guidance) and # 3 (Working Examples)

158. The patents provide only one sentence on how to determine the molecular weight of copolymer-1: "The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12)." (PTX 1, col. 3:6-8.) There are no working examples, and there is no other direction or guidance on how to calibrate the SEC column to make the same copolymer-1 that is claimed. As in *Enzo*, "the teachings set forth in the specifications provide no more than a 'plan' or 'invitation' for those of skill in the art to experiment...they do not provide sufficient guidance or specificity as to how to execute that plan." *Enzo*, 188 F.3d at 1374. The

one-sentence molecular weight disclosure is particularly egregious given that Teva had possession of detailed molecular weight calibration procedures, including specific calibration standards that it considered to be the "best." (DTX 1701; DTX 999A at TEV001222421-RC; DTX 3510 at TEV001116323.)

Factors #5 (State of Art) and # 7 (Predictability of the Art)

159. "[T]he chemical arts have long been acknowledged to be unpredictable." *Boston Sci. Corp. v. Johnson & Johnson, Inc*., 679 F. Supp. 2d 539, 557 & n.36 (D. Del. 2010) (citing *Spectra-Physics, Inc. v. Coherent, Inc*., 827 F.2d 1524, 1533 (Fed. Cir. 1983), *aff'd*, 647 F.3d 1353 (Fed. Cir. 2011)). Moreover, there is no prior art that provides any specific guidance on making the claimed invention, because the claimed molecular weight ranges are relative to the SEC standards chosen by the patentees, which were not disclosed.

Factor # 4 (Nature of Invention) and # 8 (Breadth of Claims)

160. Teva is asserting composition and method claims relating to copolymer-1, which is a polypeptide mixture of extreme complexity and heterogeneity. (July Tr. 28:8-13 (Pinchasi); DTX 1744 at TEV1017878.) Copolymer-1 contains molecules of variable length and structure, which means there will be variation in both molecular weight and behavior in an SEC column. (Sept. Tr. 1200:5-18 (Scandella); Sept. Tr. 1812:14-22 (Wall).) Teva explained the complexity of copolymer-1 to the FDA:

> Because the glatiramer acetate in Copaxone® is not a single molecular entity, but rather a heterogenous polypeptide mixture that contains a huge, perhaps incalculable number of active amino acid sequences ('epitopes') in a defined range of molar ratios, FDA has long recognized that 'Copolymer-1 [Copaxone®] is not a conventional drug, either in chemical composition or in its presumed mechanism of action.'

(DTX 1738 at KRULL0000024-25.)

161. Because Teva argues the asserted claims cover Copaxone, (Sept. Tr. 1471:12-17; 1473:14-18; 1474:24-1475:6; 1475:20-23; 1477:4-9), the specification must enable one of skill in the art to make Copaxone. *See AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) ("[A]s part of the *quid pro quo* of the patent bargain, the applicant's specification must enable one of ordinary skill in the art to practice the full scope of the claimed invention."). Teva's Citizen Petition admits that the specification does not do so:

> [T]he clinically active polypeptide sequences in Copaxone® (glatiramer acetate injection) have not been sufficiently well defined to enable an ANDA or 505(b)(2) applicant to conclusively demonstrate that the clinically active polypeptide sequences in its purported generic product are qualitatively and quantitatively "the same as" those in Copaxone®.

(DTX 1738 at KRULL0000020.) [redacted]

[redacted] Indeed, Teva initially alleged in this case that because Copaxone is "extremely difficult to duplicate," Sandoz must have "used Teva Ltd.'s trade secrets to develop Sandoz's generic glatiramer acetate product and to prepare and file the Sandoz, Inc. ANDA." (Complaint ¶¶ 74, 80.)

162. "[I]n cases involving unpredictable factors, including the chemical arts, courts have 'refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim.'" *Glaxo Wellcome Inc. v. Eon Labs Mfg.*, No. 00 Civ. 9089 (LMM), 2002 U.S. Dist. LEXIS 14950, at *10 (S.D.N.Y. Aug. 13, 2002) (quoting *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75

F.3d 1558, 1564 (Fed. Cir. 1996)). Accordingly, the asserted patents should be held invalid for lack of enablement.

III. THE ASSERTED CLAIMS ARE INVALID FOR INDEFINITENESS

163. The Court has construed "'copolymer-1 having a molecular weight'" to mean "'copolymer-1 having a peak molecular weight detected using an appropriately calibrated suitable gel filtration column.'" (Claim Construction Order at 40 n.10.) The Court has construed "average molecular weight" to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (*Id.* at 40.)

164. There are several qualities that one of ordinary skill in the art in 1994 would have considered when deciding whether an SEC calibration standard was appropriate. (Sept. Tr. 1292:4-12 (Scandella).) "One quality is that they should have a well-defined molecular weight. They should be commercially available. They should have a hydrodynamic volume which is close to the hydrodynamic volume of the sample being analyzed." (Sept. Tr. 1292:8-11 (Scandella).) It is not necessary for the standards to have the same hydrodynamic volume as the sample being analyzed. (Sept. Tr. 1292:13-15 (Scandella).) As Dr. Scandella testified:

> Often one doesn't know what the hydrodynamic volume of a sample is, and in the biotechnology industry size exclusion chromatography is used normally using protein standards, and one reports the results as relative to the protein standards, understanding that the shape of the molecule that you're studying may not be exactly the same as the protein standards.

(Sept. Tr. 1292:15-20 (Scandella).)

165. Using an "appropriate calibration" does not mean that one will get an absolute molecular weight of copolymer-1 using SEC, because "SEC doesn't yield absolute molecular weights. It's not an absolute measurement method. So one wouldn't assume that the value that came from a size exclusion column was an absolute value." (Sept. Tr. 1292:21-1293:1 (Scandella); 1825:1-4 (Wall).)

166. The asserted claims with "molar fraction" or "species" limitations require the use of SEC calibration standards for molecular weight determination. (Sept. Tr. 1224:22-1227:4 (Scandella).)

167. In 1994, there were multiple ways to appropriately calibrate an SEC column, and it is unlikely that the different calibrations would have yielded the same peak molecular weight for copolymer-1:

> Q. Based on your experience and the documents you've reviewed in this case, would a person of ordinary skill in the art have gotten the same answer for molecular weight of copolymer-1 regardless of which appropriate standard was chosen?
>
> A. No. We've seen that that's not the case.

(Sept. Tr. 1293:3-7 (Scandella); 1824:3-25 (Wall).)

168. Under the Patent Act, the patent claims must "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, ¶ 2. "The primary purpose of the definiteness requirement is to ensure that the claims are written in such a way that they give notice to the public of the extent of the legal protection afforded by the patent, so that interested members of the public, *e.g.*, competitors of the patent owner, can determine whether or not they infringe." *Default Proof Credit Card Sys. v. Home Depot U.S.A., Inc.*, 412 F.3d 1291, 1302-03 (Fed. Cir. 2005) (quoting *All Dental Prodx LLC v. Advantage Dental Prods.*, 309 F.3d 774, 779-80 (Fed. Cir. 2002)).

169. In August 2011, the Federal Circuit held that "a construed claim can be indefinite if the construction remains insolubly ambiguous, meaning it fails to provide sufficient clarity about the bounds of the claim to one skilled in the art." *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, No. 2010-1183, 2011 U.S. App. LEXIS 17826, at *19 (Fed. Cir. Aug. 26, 2011).

170. Because there was more than one way to appropriately calibrate an SEC column in 1994, and the resulting molecular weights would not have been the same, the term "appropriately calibrated suitable gel filtration column" in the Court's claim construction remains insolubly ambiguous. (Sept. Tr. 1293:3-7 (Scandella); 1824:3-25 (Wall).) Accordingly, the following claims, all of which contain the limitation "copolymer-1 having a molecular weight" or "average molecular weight" or are "molar fraction" or "species" claims, are indefinite:

U.S. Patent No. 5,800,808: Claim 1

U.S. Patent No. 5,981,589: Claim 1

U.S. Patent No. 6,054,430: Claims 1 and 2

U.S. Patent No. 6,342,476: Claim 1

U.S. Patent No. 6,362,161: Claim 1

U.S. Patent No. 6,620,847: Claims 1 and 6

U.S. Patent No. 6,939,539: Claims 1, 8, 9, 10, 12, 23, 30, and 31

U.S. Patent No. 7,199,098: Claims 1 and 8

IV. THE ASSERTED CLAIMS ARE INVALID AS OBVIOUS

A. Findings of Fact on Obviousness

1. Background of Copolymer-1 and the Claimed Invention

171. Copolymer-1 was discovered at the Weizmann Institute in Israel by Drs. Michael Sela, Ruth Arnon, Dvora Teitelbaum, and others beginning in 1966 and culminating with the submission of their discovery to the *European Journal of Immunology* in March 1971. (July Tr. 309:8-311:8; PTX 499 ("1971 Teitelbaum").) One month later, the Weizmann inventors filed a patent application, which ultimately issued as U.S. Patent No. 3,849,550 ("the '550 patent"). (PTX 26.) The Weizmann inventors recognized their discovery as a "treatment or a prevention

of certain autoimmune diseases affecting the brain" such as experimental allergic encephalomyelitis ("EAE"), which, according to the patent, "serves as a model disease for multiple sclerosis. . . ." (PTX 26, '550 patent, col. 1:14-16; 28-30.)

172. The Weizmann scientists' '550 patent issued in 1974. (PTX 26.) Before expiration of the '550 patent, Dr. Murray Bornstein conducted clinical trials between 1980 and 1985 confirming that copolymer-1 provided a "very significant reduction in relapse rates" in multiple sclerosis patients and "slow[ed] down progression of disability." (Testimony of Irit Pinchasi; July Tr. 23:17-24:1; 268:23-269:1.) Dr. Bornstein's main clinical study performed in the United States was called the BR-1 study. (July Tr. 22:4-24.) Results from the BR-1 study were presented at the 37th Annual Meeting of the American Academy of Neurology in Dallas, Texas from April 30, 1985 to May 2, 1985. Dr. Bornstein, along with Drs. Teitelbaum, Arnon, Sela, and others, published the results of the BR-1 study in 1987 in the *New England Journal of Medicine*. (PTX 31; July Tr. 327:22-328:13.) The published study describes copolymer-1 as a composition "synthesized by the random polymerization of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine in the ratio of 6.0: 1.9: 4.7: 1.0 (molecular weight, 14,000 to 23,000)." (PTX 31 at 408.) [redacted]

173. Plaintiff Yeda Research and Development Co. Ltd. is the licensing arm of the Weizmann Institute. (Complaint in Case. No. 08-cv-7611 ¶ 4.) [redacted]

[redacted]

174. Teva began its work on copolymer-1 under its agreement with Yeda in 1986. (DTX 1023 at TEV00000453.) That year, Dr. Irit Pinchasi became Teva's project manager for Teva's copolymer-1 project. (July Tr. 9:21-11:21.)

175. The '550 patent expired November 18, 1991. (PTX 26.) One month earlier, in October 1991, Teva began enrolling patients in a second clinical trial, sometimes called the "01-9001 trial," "9001 trial," "the Johnson study," or the "Johnson 9001 study." (Sept. Tr. 106:21-107:22; July Tr. 78:11-13; 268:23-269:5.) The results of the Johnson study were presented at the annual meeting of the American Neurological Association in San Francisco, California, in October 1994 and were published in July 1995 in *Neurology*. (PTX 597 at 1268.) In addition to the lead author, Dr. Kenneth Johnson, co-authors included two witnesses at trial – Dr. Irit Pinchasi (*id*. at 1276) and Dr. Robert Lisak (*id.* at 1268). The Johnson paper described copolymer-1 as "a mixture of synthetic polypeptides composed of four amino acids, L-alanine, L-glutamic acid, L-lysine, and L-tyrosine, in a molar ratio of 4.2, 1.4, 3.4, and 1.0, respectively, and with an average molecular weight 4,700 to 13,000 daltons." (PTX 597 at 1269.) The

material used in the Johnson study was manufactured by Teva. (DTX 1023 at TEV000000490.) The 4,700 to 13,000 dalton molecular weight range of the copolymer-1 used in the Johnson study matched the molecular weight range for which Teva originally sought FDA approval in its NDA for Copaxone, which was filed in 1995, a year after the application leading to the patents-in-suit. (DTX 1023 at TEV000000461; July Tr. 87:9-12.)

176. Teva filed a patent application for what it called "Copolymer-1 Improvements in Compositions of Copolymers" on May 24, 1994. (PTX 11.) The originally named inventors included three Teva employee witnesses who testified at trial either live or through deposition designations: Irit Pinchasi, Eliezer Konfino, and Haim Varkony. (PTX 11 at TEV000309434.) A fourth Teva employee, an analytical chemist named Dr. Ilan Schwartz, was originally named as an inventor and was identified as one of four Teva employees who were present on May 24, 1994, when the patent application was prepared. (*Id.*; DTX 1389 at 46:1-20, 85:19-26; DTX 1393 at 21:7-11.) The May 24, 1994 application is a common parent application to all nine patents-in-suit. (PTX 1-9.) During prosecution, Drs. Teitelbaum, Arnon, and Sela were added as inventors. (PTX 1-9.) All Teva inventors except for Mr. Konfino were removed from the patents as inventors. (*Id.*)

177. Dr. Ruth Arnon, an author of the 1971 Teitelbaum paper, an inventor of the '550 patent, an author of the 1987 Bornstein article in the *New England Journal of Medicine*, and a named inventor of the patents-in-suit, testified that she discovered that the range of 5 to 9 kDa was "optimal" for preventing EAE and not causing degranulation in RBL cells. (July Tr. 333:7-17.)

178. Dr. Irit Pinchasi testified that her team at Teva discovered copolymer-1 with an "optimum" molecular weight ranges for active and nontoxic material, which was different than

prior art copolymer-1. (July Tr. 41:25-42:13; 65:3-25.) She supported her testimony with references to Teva data dated May 4, 1988. (PTX 36; July Tr. 63:23-65:25.) The very next day, she wrote to Dr. Murray Bornstein, stating that she had discovered "a very 'narrow window' in which you have a relatively high chance of getting a non-toxic and active material" corresponding to the molecular weight range of "8000-12,000 by ultracentrifugation." (DTX 1200 at 1.)

179. In its pretrial brief, Teva described the work of the inventors of the patents-in-suit as optimizing the molecular weight ranges for copolymer-1. (Teva August 29, 2011 Pretrial Brief at 3 ("Drs. Sela and Arnon and their colleague Dr. Dvora Teitelbaum at the Weizmann Institute, in collaboration with Eliezer Konfino and others at Teva, made the discovery that the higher toxicity of certain batches of copolymer-1 was correlated with both a greater percentage of high molecular weight species and a higher average molecular weight. . . . They found that there was an optimal molecular weight distribution that minimized toxicity while retaining activity.").)

180. Notwithstanding their claim that they discovered an optimum, reduced toxicity molecular weight range for copolymer-1, Teva filed a New Drug Application ("NDA") with the Food and Drug Administration ("FDA") on June 5, 1995, seeking to market copolymer-1 with a molecular weight range of 4,700 to 13,000 for slowing progression of disability and reducing frequency of relapses of patients with multiple sclerosis. (DTX 1073; DTX 1023 at TEV000000461; July Tr. 87:9-12.) The FDA approved Teva's NDA on December 20, 1996 for copolymer-1 containing the amino acids L-glutamic acid, L-alanine, L-tyrosine, and L-lysine, with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively, and with an average molecular weight between 4,700 and 11,000 daltons. (DTX 1073 at TEV000104078.)

181. Teva relied on the Bornstein BR-1 clinical trial data to support its NDA for Copaxone.(July Tr. 268:23-269:12.) Because the molecular weight of the copolymer-1 used in the Bornstein BR-1 clinical trials was reported to be higher than the molecular weight for which Teva sought FDA approval, Teva sought to convince the FDA that the higher-molecular-weight copolymer-1 in the Bornstein BR-1 study was comparable to the lower molecular weight copolymer-1 manufactured by Teva. (*Id.* at 269:21-270:6.) (*See also, infra* ¶¶ 193-203.)

182. By the time Teva's NDA was approved, "glatiramer acetate" had become the scientific name for "copolymer-1." (DTX 1073 at TEV000104078 ("COPAXONE® is the brand name for glatiramer acetate (formerly known as copolymer-1).".)

2. The Scope and Content of the Prior Art

a. U.S. Patent No. 3,849,550 and 1971 Teitelbaum

183. The patents-in-suit cite to both the 1971 Teitelbaum article and '550 patent as part of the "Background of the Invention" section. (PTX 1, col. 1:23-26.)

184. According to the PTO, the '550 patent describes a method of "treating multiple sclerosis (column 1, line 30) with copolymer-1 having a molecular weight of more than 10,000 (column 1, line 62) but not more than 25,000 (see the fourth line of claim 1)." (PTX 17 at TEV000304219; *see also* PTX 15 at TEV000309109 (noting the '550 patent "discloses Copolymer-l having a preferred molecular weight range of 10,000 or more . . . ."); PTX 17 at TEV000304219 ("[The '550 patent] disclose[s] treating multiple sclerosis . . . with copolymer-1 having a molecular weight of more than 10,000 (column 1, line 62) but not more than 25,000. . . ."); PTX 18 at TEV000310336; PTX 19 at TEV000304449.) Teva did not dispute these characterizations of the '550 patent during prosecution of the patents-in-suit and agreed that "[t]he '550 patent teaches copolymer-l with a minimum molecular weight of 10 kilodaltons." (PTX 18 at TEV000310449; see also PTX 15 at TEV000309118; PTX 17 at TEV000304384.)

185. The ’550 patent cites on its face only one journal article – the 1971 Teitelbaum publication submitted by Drs. Teitelbaum, Arnon, and Sela to the *European Journal of Immunology* one month earlier in March 1971. (PTX 26, ’550 patent, col. 4:31; PTX 499 at 248.) The specification of the ’550 patent states that “Copolymers according to the present invention are easily prepared by conventional procedures.” (PTX 26, ’550 patent, col. 2:53-54.) The specification of the ’550 patent then gives a description of how the copolymers described therein, including copolymer-1 were prepared. (*Id.* at col. 2:54-64.)

186. The 1971 Teitelbaum article expressly identifies copolymer-1 and notes that the “average molecular weights of the polymers were determined, in a Spinco model E ultracentrifuge, from sedimentation and diffusion measurements . . . .” (PTX 499 at 243 § 2.3.1 and Table 1; 244 § 3.7.)

187. According to Dr. Ruth Arnon, molecular weight measurements at the Weizmann Institute were always done the same way because it had only one ultracentrifugation machine at the time that it was making copolymer-1. (July Tr. 343:4-345:9.)

188. Dr. Carl Scandella testified, and no one disputed, that one of skill in the art would understand that the reference in the ’550 patent to a copolymer-1 with a molecular weight of 10 kDa refers to molecular weight determined by ultracentrifugation based on the related 1971 Teitelbaum article. (Sept. Tr. at 1288:9-1290:2.) Dr. Scandella further testified that the particular type of ultracentrifugation described in the 1971 Teitelbaum article (using sedimentation and diffusion measurements from a Spinco model E ultracentrifuge) would provide a “weight average” molecular weight. (*Id.* at 1290:6:10.) No Teva expert disputed Dr. Scandella’s conclusion, and Teva’s Dr. Gregory Grant expressly agreed that the 1971 Teitelbaum article obtained its molecular weight values by use of ultracentrifugation. (*Id.* at 1440:3-25.)

189. Teva's expert, Dr. George Gokel agreed that the '550 patent and 1971 Teitelbaum article informed those of skill in the art how to make copolymer-1. (Sept. Tr. 388:6-389:8.) Dr. Gokel relied on specific examples in the 1971 Teitelbaum article to form his infringement opinion. (Sept. Tr. at 388:23-391:20.)

> Q. Now, does the literature concerning copolymer-1 include the Weizmann Institute's '550 patent?
>
> A. The '550 patent relates to polymers of that type, but I don't think copolymer-1 is named in the '550 patent.
>
> Q. There's no reference -- could you turn to document 26 in your -- and you may well be right, so perhaps the better question, sir, is copolymer-1 one of the copolymers that is included in the 550 Weizmann Institute patent?
>
> A. The patent describes polymers that have alanine, glutamic acid, lysine and tyrosine, and they claim weights, molecular weights between 15,000 and 25,000.
>
> Q. And when was that patent issued, sir?
>
> A. November 19, 1974.
>
> Q. Now, that patent, it also describes a synthesis method for making such copolymers, correct?
>
> A. Well, it describes that they were synthesized.
>
> Q. Specifically, could you look at column 2, lines 53 to 63?
>
> A. Yes, I have it.
>
> Q. Okay. And does it describe there the synthesis of a protected copolymer using diethylamine as an initiator in the presence of dioxane?
>
> A. It doesn't give any experimental details, but it gives a general approach.
>
> Q. Yes and it includes diethylamine as an initiator in the presence of dioxane?
>
> A. Yes, it does.

Q. Does it also describe using N carboxyanhydrides to tyrosine, alanine, glutamic acid and lysine?

A. Yes, it does.

Q. Does it describe using a benzyl protecting group on the glutamic acid?

A. Yes it does.

Q. Does it describe using trifluoroacetyl as a protecting group for the lysine?

A. Yes.

Q. Does the ’550 patent describe deprotecting the glutamic acid by using hydrogen bromide in acetic acid?

A. It describes only deprotecting with hydrogen bromide.

Q. That was my question, sir. Does the ’550 patent describe deprotecting the lysine by using piperdine?

A. Yes. I’m sorry, I misunderstood. I pronounce it piperdine. Yes.

Q. And you testified at length about the ’808 patent I think on your direct testimony. You gave a lot of testimony concerning the ’808 patent, correct?

A. I testified about the ’808 patent.

Q. Are you aware that it specifically says that the copolymer-1 according to the present invention of the ’808 patent may be prepared by methods known in the art, for example the process disclosed in U.S. Patent No. 3849550?

A. Yes.

Q. And that literature also includes the Teitelbaum article that we discussed so much yesterday and today, is that right, Exhibit 499?

A. That’s correct.

Q. And that article, which is also back in the 1970’s, of course, it has the same disclosure about how to synthesize copolymer, correct?

A. The same disclosure as what?

> Q. As in the ’550 patent.
>
> A. It discloses a synthetic method. I don’t know if it has the same details in it.
>
> Q. Do you recall that in fact it has even more details, that the Teitelbaum article describes the quantities of the amino acids that are used in the starting material, correct?
>
> A. That may be so.

(Sept. Tr. 523:3-525:18.)

190. Mylan’s expert Dr. Zeiger testified that the ’550 patent describes copolymer-1 compositions with average molecular weights between 10 and 25 kDa. (Sept. Tr. 841:19-842:6.) Dr. Zeiger provided extensive teaching regarding how to make copolymer-1, as described in the ’550 patent. (Sept. Tr. 819:7-826:15.)

191. Teva is expected to argue that the use of HBr in acetic acid to cleave peptide bonds is a point of novelty of the asserted claims. Dr. Trevor Laird testified that it was well known at the time of the invention to use HBr in acetic acid to cleave peptide bonds. (Sept. Tr. 1138:16-22, 1139:10-21, 1140:9-1141:16, 1143:1-1144:11, 1147:7-1148:9.) Teva’s expert Dr. Sampson also agreed that multiple publications available prior to 1994 would have allowed a person of skill in the art to conclude that use of HBr in acetic acid resulted in peptide bond cleavage. (Sept. Tr. 1663:25-1664:10, 1666:12-19 (referring to DTX 3329),1666:20-1667:21, (referring to DTX 3327), 1668:19-1669:9 (referring to DTX 1781), 1670:2-20 (referring to DTX 1783).)

192. Teva’s expert Dr. Grant testified that the ’550 patent does not teach copolymer-1 compositions with an average molecular weight of 10,000 daltons. This testimony was not credible. The ’550 patent expressly describes the copolymers described in the specification of that patent as “being in excess of 10,000 and preferably above about 18,000.” (PTX 26 at col.

1:62-63.) Moreover, Teva repeatedly told the PTO that the '550 patent teaches a copolymer-1 composition with a minimum molecular weight of 10,000 daltons. (PTX 13 at TEV000304151; PTX 15 at TEV000309118; PTX 17 at TEV000304384.) When confronted with Teva's statements in the prosecution history that the '550 patent teaches a copolymer-1 with a minimum molecular weight of 10 kilodaltons, Dr. Grant stated his conclusion that Teva's statements to the PTO did not contradict his opinion, but he provided no evidence to support his conclusion:

> Q. I want to ask you a little about the '550 patent. As I heard your direct testimony, your opinion is that the '550 patent does not disclose copolymer-1 with a molecular weight of 10 kilodaltons, is that correct?
>
> A. That's correct.
>
> Q. And it's true, isn't it, that in the prosecution of the patents in this case, Teva took the exact opposite view, isn't that right?
>
> A. I don't agree.

(Sept. Tr. 1482:16-24; *see also* 1482:25-1483:24.)

b. Murray Bornstein, *A Pilot Trial of Cop-1 In Exacerbating-Remitting Multiple Sclerosis*, 317 (No. 7) New England Journal of Medicine 408 (1987)

193. Dr. Bornstein's 1987 article in the New England Journal of Medicine (PTX 31) reported the results of the Bornstein BR-1 clinical trial and disclosed the use of copolymer-1 with an average molecular weight between 14,000 and 23,000 daltons to treat MS. (PTX 31 at 408.) [redacted] The copolymer-1 in that study was "not toxic in animals," and had less than 30% serotonin release in the RBL test. (*Id.* at 408-409.)

194. Teva's NDA described the BR-1 study as follows:

> The first pivotal clinical study with copolymer-1 was performed under the supervision of M. Bornstein MD, at the Albert Einstein College of Medicine, New York, USA. The study is known as the Bornstein trial, and is referred to as study BR-1 in the clinical and statistical sections of this application. The copolymer-1 used was manufactured in an academic environment at the Weizmann Institute of Science and at Bio-Veda, (MILES) Israel. The study indicated that daily subcutaneous injection of 20 mg of copolymer-1 produces a significant clinical therapeutic effect in the initial relapsing-remitting (R-R) phase of multiple sclerosis (see the controlled clinical studies section). Because multiple sclerosis is a severely debilitating disease with limited treatment options, the Bornstein results with copolymer-1 represented a major therapeutic gain.

(DTX 1023 at TEV000000453.)

195. Teva told the FDA that it replicated the Bornstein BR-1 trial with the Johnson 9001 trial.

> The Copolymer-1 for Injection for which approval is being requested was fully evaluated for use in R-R multiple sclerosis (see the controlled clinical studies section of this application). The results of the Bornstein clinical trial were replicated in a controlled, double-blind phase III clinical study involving two hundred and fifty-one patients in eleven centers in the USA (protocol #01-9001).

196. Teva relied on the similarity between the Bornstein BR-1 trial and the Johnson 9001 trial to get FDA approval for Copaxone. (July Tr. 269:10-12, 21-23.) Specifically, Teva argued to the FDA that the copolymer-1 in the Bornstein BR-1 trial, the Johnson 9001 trial, and Copaxone were all comparable:

> Presented here is a summary which demonstrates that copolymer-1 drug substance batches used in the two pivotal clinical studies, BR-1 and 01-9001, and the copolymer-1 drug substance which will be included in the marketed Copaxone® are comparable. The copolymer-1 used in study BR-1 was manufactured at the Weizmann Institute of Science and its sub-contractor BioYeda (Israel), prior to the involvement of TEVA Pharmaceutical Industries Ltd. The copolymer-1 drug substance used in study 01-

> 9001 was manufactured by TEVA Plantex on a pilot plant scale, under cGMP conditions.

(DTX 1028 at TEV000002324.)

197. [redacted]

3. Differences Between the Claimed Invention and the Prior Art

198. To the FDA, Teva represented that the copolymer-1 described in the Bornstein BR-1 study was comparable to the copolymer-1 for which Teva ultimately obtained FDA approval to market and which Teva claimed at trial was covered by the patents-in-suit. To the PTO, Teva was required to show that the copolymer-1 in the Bornstein BR-1 study was patentably distinct from the copolymer-1 compositions and methods for making those compositions claimed in the patents-in-suit.

199. The purported differences between the claims of the patents-in-suit and the prior art is that the copolymer-1 claimed in the patents-in-suit has a lower molecular weight and exhibits surprisingly less toxicity than copolymer-1 with higher molecular weights.

200. The copolymer-1 described in the patents and the copolymer-1 publicly used in the Bornstein BR-1 study had little differences. The Bornstein paper specifically notes Dr.

Bornstein chose batches of copolymer-1 with less than 30% RBL degranulation "to reduce inflammatory reactions at injection sites." (PTX 31 at 409.) [redacted]

201. Teva's original NDA for Copaxone sought FDA approval to market copolymer-1 with an average molecular weight ranging from 4,700 daltons to 13,000 daltons. (DTX 1023 at TEV000000461; July Tr. 87:9-12.) That range of molecular weights encompassed copolymer-1 compositions within the prior art. Teva's NDA made no distinction between the toxicity of copolymer-1 at either end of the range.

202. Teva later reduced Copaxone's molecular weight range from 5,000 to 9,000 daltons. [redacted]

203. Dr. Pinchasi admitted at trial that the Bornstein BR-1 study and the Johnson 9001 study did not show differences in the side effects among patients who received the copolymer-1 with a higher molecular weight in the Bornstein BR-1 study and those who received a lower molecular weight copolymer-1 in the Johnson 9001 study. (July Tr. 265:17-266:25.)

4. The Person of Ordinary Skill in the Art

204. The patents-in-suit define the claimed invention in terms of a relationship between lower molecular weight and lower toxicity. (*See, e.g.*, PTX-1.) As a result, there are at

least two different fields of art relevant to the asserted patents: characterization of the molecular weight of polymers, and toxicity.

205. Dr. Grant defined one of ordinary skill in the art as a person with an advanced degree or something equivalent in a chemical or biological discipline, significant experience in the synthesis or characterization of polymers, including proteins or synthetic peptides, and access other scientists having related and/or complementary knowledge and experience in the areas of polymer chemistry, biochemistry, analytical chemistry, separation technology, medicine, and toxicology. (Sept. Tr. 189:22-190:6; PTX-986, at 3.) Drs. Gokel and Sampson agreed with Dr. Grant's definition. (Sept. Tr. 351:16-352:2 (Grant); Sept. Tr. 1635:16-18 (Sampson).)

206. At trial, Dr. Scandella adopted the definition of a person of ordinary skill in the art contained in his expert report. (Sept. Tr. 1190:16-20.) In his report, Dr. Scandella defined a person of ordinary skill in the art of size exclusion chromatography as it relates to the asserted patents as a person with a Ph.D. in chemistry, biochemistry or related field, with a minimum of three years of experience in chromatography, and specifically in size exclusion chromatography of macromolecules, or a person with a minimum of five years experience directing a research laboratory that conducts chromatography.

207. Dr. Wall defined a person of ordinary skill as someone with a PhD in chemistry, biochemistry or a related field with three years of experience in chromatography, or a person who has supervised or directed a research lab that conducts chromatography. (Sept. Tr. 1756:4-12.)

208. Dr. Zeiger opined that a person of ordinary skill in the fields of biochemistry and immunology in 1994 would have had an advanced degree in a chemical or biological discipline and extensive experience in the synthesis, fractionation and characterization of polymers, such as

their hydrodynamic and structural properties as applied to proteins, sympathetic peptides and/or polydispersed peptide mixtures, as well as experience in the determination of the molecular weight distribution and average molecular weights of such polymers by methods such as size exclusion chromatography and an understanding of how the standards and the conditions used in the molecular weight determination affect the results obtained. (Sept. Tr. 809:10-810:5)

209. Dr. Kent opined that a person of ordinary skill in the art "would have an advanced degree or equivalent in a chemical or biological discipline and significant experience in one or more of the following areas: The synthesis, fractionation or characterization of peptide polymers such as their amino acid composition and/or hydro dynamic and structural properties as applied to proteins, synthetic peptides and/or poly disperse mixtures." (Sept. Tr. 652:4-17.)

210. Drs. Rice, Laird and Kimber also provided opinions as to the definition of a person of ordinary skill in the art. (Sept. Tr. at 1008:7-12 (Rice); Sept. Tr. 1122:1-10 (Laird); July Tr. 375:18-20. (Kimber).)

211. None of the definitions of a person of ordinary skill in the art were meaningfully different. No expert from any of the parties suggested that their testimony would differ if they applied the definition of ordinary skill in the art provided by another witness.

5. Prima Facie Obviousness Considerations

212. The asserted claims for eight of the nine patents-in-suit include a limitation that the molecular weight of the claimed copolymer-1 fall within a certain range.

about 5 to 9 kDa – '808 patent, PTX 1

about 5 to 9 kDa – '589 patent, PTX 2

75% between 2 and 20 kDa – '430 patent, PTX 4

75% between 2 and 20 kDa – '476 patent, PTX 5

75% between 2 and 20 kDa – '161 patent, PTX 6

about 4 to about 9 kDa – ’847 patent, PTX 7

about 4 to about 9 kDa – ’539 patent, PTX 8

75% between 2 and 20 kDa – ’098 patent, PTX 9

213. The ranges described in the patents-in-suit either overlap with or are adjacent to the ranges in the ’550 patent. The ’550 patent describes copolymer-1 with a minimum molecular weight range of 10-25 kDa. The ’808, ’589, ’847, and ’539 patents claim a copolymer-1 with an average molecular weight up to “about” “9 kilodaltons.” The ’430, ’476,’161, and ’098 patents claim copolymer-1 compositions with a percentage of their molar fraction between 2 and 20 kDa.

214. The reported molecular weight values in the ’550 patent are weight average molecular weight values determined by ultracentrifugation. (*See, e.g.,* Section I.B, *supra*.)

215. A batch of copolymer-1 with a weight average molecular weight of 10 kDa would have a peak molecular weight that either falls within the ranges of the claims, or abuts those ranges.[2] [redacted]

[2] Sandoz has asked the Court to reconsider its claim construction ruling of the “average molecular weight” terms to exclude any copolymer-1 composition with a weight average molecular weight in excess of 10,000 daltons. To the extent that the Court revises its claim construction, the molecular weight range of the ’550 patent will abut the claim ranges of the patents-in-suit. To the extent that the Court does not revise its claim construction, the ranges of the patents-in-suit and prior art will be overlapping.

[redacted]

216. Regardless whether the peak molecular weight of the copolymer-1 used in the Bornstein BR-1 trial had a minimum peak molecular weight of 8,000 daltons or 10,350 daltons, Teva's Dr. Grant admitted that the Mw for copolymer-1 will be higher than the Mp of the same copolymer-1, and that principle would apply to the copolymer-1 described in the prior art '550 patent. (Sept. Tr. at 1484:22-25; 1485:18-25.) He also testified that he interpreted the claim language of "about 5 to 9 kDa" to include a 10% buffer on both sides of the range, making "about 5 to 9 kDa" as broad as 4.5 to 9.9 kDa. (*Id.* at 1486:1-21.) Based on the admission by Dr. Grant regarding the general relationship between the Mw and Mp of copolymer-1, and as confirmed by the up to 1650 dalton difference between the Mp and Mw for the prior art batches used and reported in the 1987 Bornstein study, the peak molecular weight of the 10,000 dalton batch of copolymer-1 described in the '550 patent would fall within the molecular weight range of the asserted claims with molecular weight ranges. Sandoz has proven that it is highly probable (by clear and convincing evidence) that a batch of copolymer-1 with a weight average molecular weight of 10 kDa, such as the one disclosed in the '550 patent, would have a peak molecular weight of less than 9.9 kDa.

217. Dr. Rice is President of Susan A. Rice and Associates, Inc., which provides consulting services in the area of toxicology and pharmacology. (Sept. Tr. 996:1-4, 11-14.) Through her consultancy, Dr. Rice provides guidance to pharmaceutical companies on negotiating the regulatory requirements of the FDA, and performing toxicological studies for purposes of FDA review. (Sept. Tr. 996:11-24; 997:5-10.)

218. Dr. Rice received her B.S. in Biochemistry from the University of California at Davis in 1971, followed by a Ph.D. (also from U.C. Davis) in Comparative Pharmacology and Toxicology in 1976. (Sept. Tr. 991:24-992:5.)

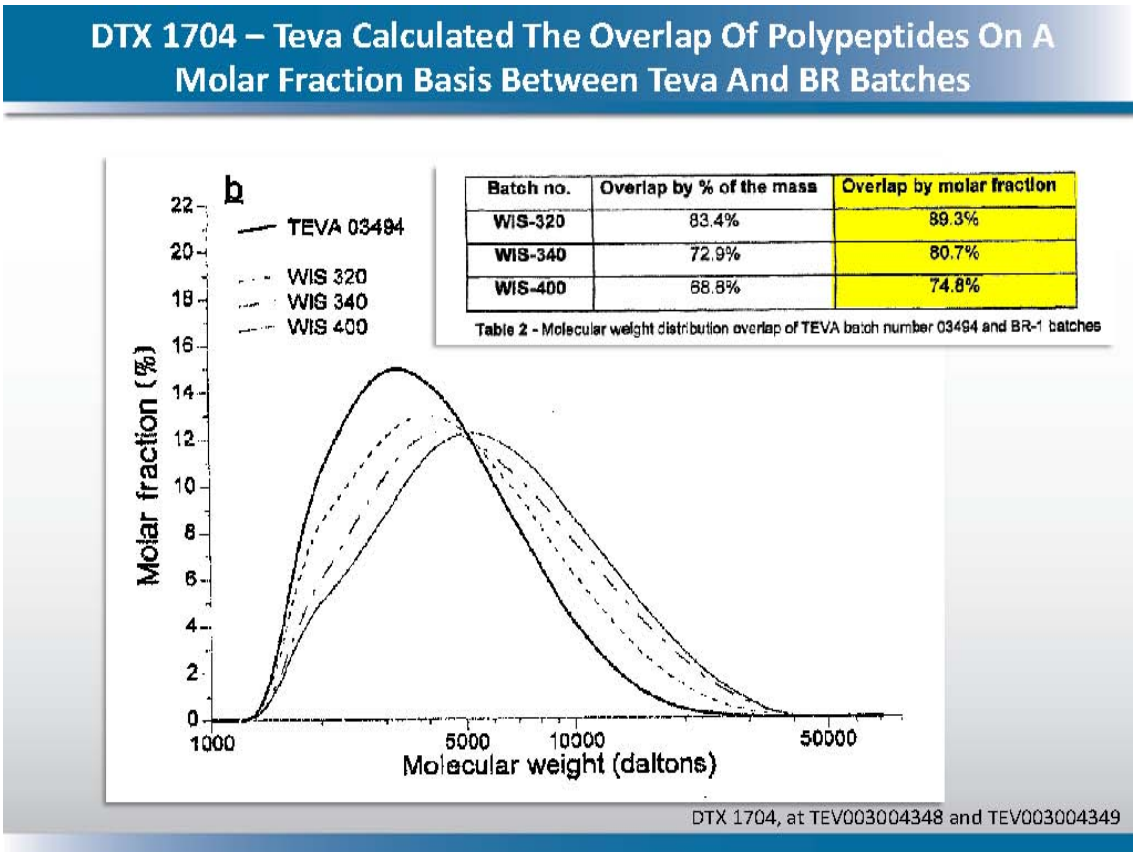
219. Dr. Rice has served as a Toxicologist for the conduct of NIH-funded research, and was an Associate Professor of Pharmacology and Toxicology at Stanford University from 1986-2002. (Sept. Tr. 994:5-24; DTX 1322.)

220. Dr. Rice has published approximately 60 articles, including 50 in peer-reviewed journals. (Sept. Tr. 998:4-9.) Dr. Rice has been a diplomate of the American Board of Toxicology since 1990. *(Id*. at 998:10-11; DTX-1322.)

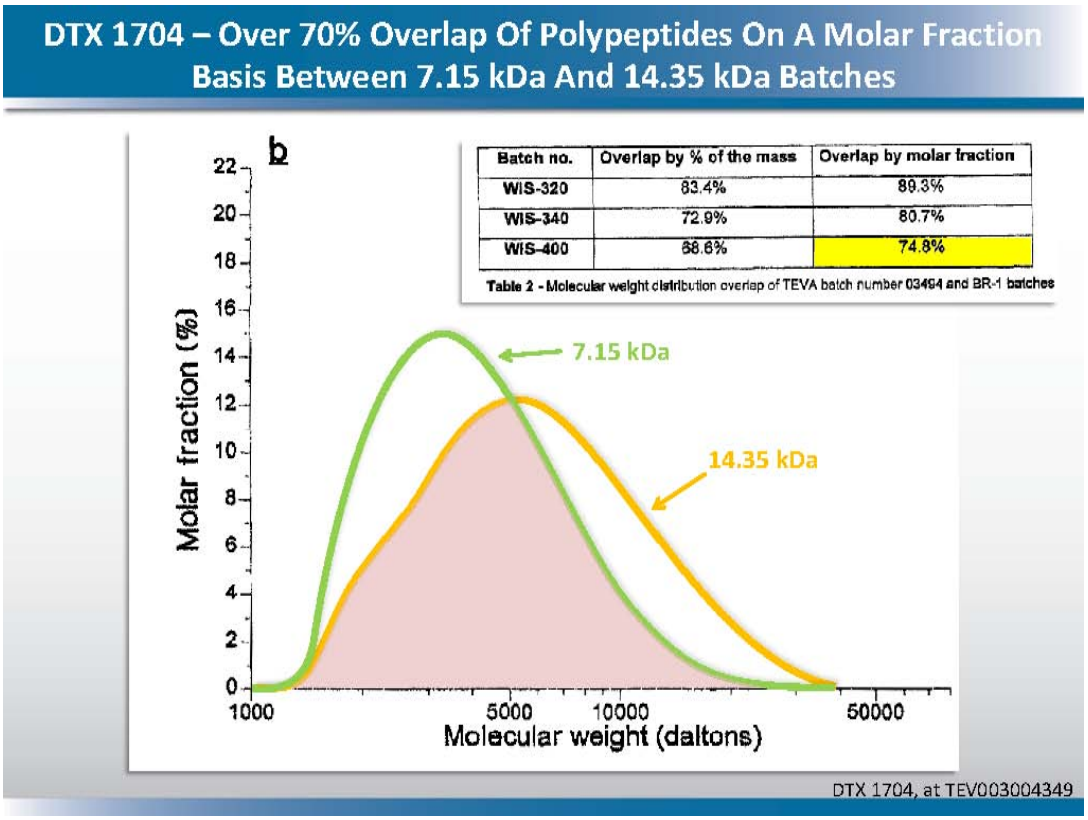
221. In a head-to-head comparison between the molecular weights described in the patents-in-suit and the molecular weights described in the '550 patent, the ranges are abutting ranges. All of Teva's ranges up to 9 kDa are qualified by the word "about." A range of batches of copolymer-1 of 4.5 to 9.9 kDa abuts a range of 10 kDa to 25 kDa, as described in the '550 patent. To the extent that there is a gap in molecular weights between 9.9 kDa and 10 kDa, Dr. Susan Rice testified that she would not expect any significant difference in the toxicity profile when comparing copolymer-1 batches described at the upper end of the ranges of the patents-in-suit and the lower end of the range disclosed in the '550 patent. (Sept. Tr. 1013:8-1015:17.) Dr. Rice, an expert toxicologist, testified that she has extensive experience evaluating the toxicity profile of polymers in different molecular weight ranges. (Sept. Tr. 1015:1-10.)

222. Dr. Alan Zeiger also testified regarding the difference in molecular weight profile between the patents-in-suit and the prior art. Dr. Zeiger reviewed the molecular weight profiles of batches of copolymer-1 with peak molecular weights between 7,150 daltons and 14,350 daltons and testified that there is "a considerable amount of overlap" in those profiles. (Sept. Tr.

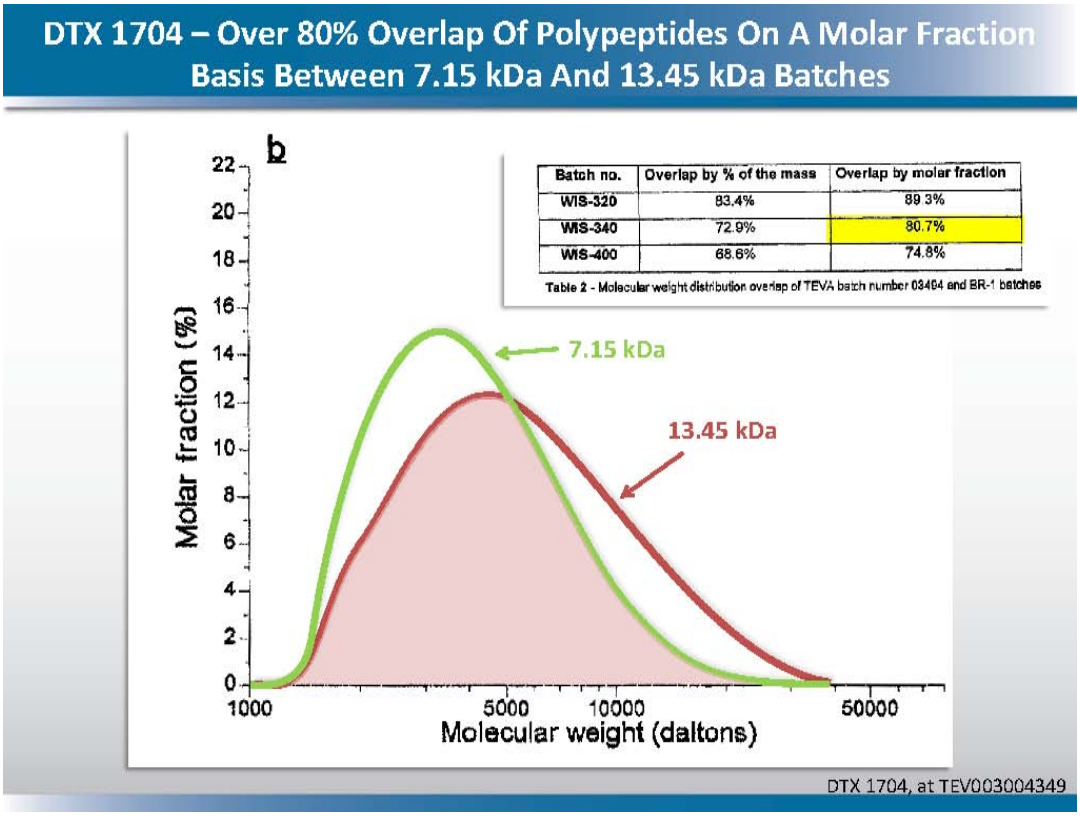
875:7-8, 11-18; 879:24-880:13; DTX-4030 at 11-13.) Dr. Zeiger defined that overlap on the basis of molar fraction as "a percent of a given size of molecule" that the two batches have in common. (Sept. Tr. 869:4-9.)



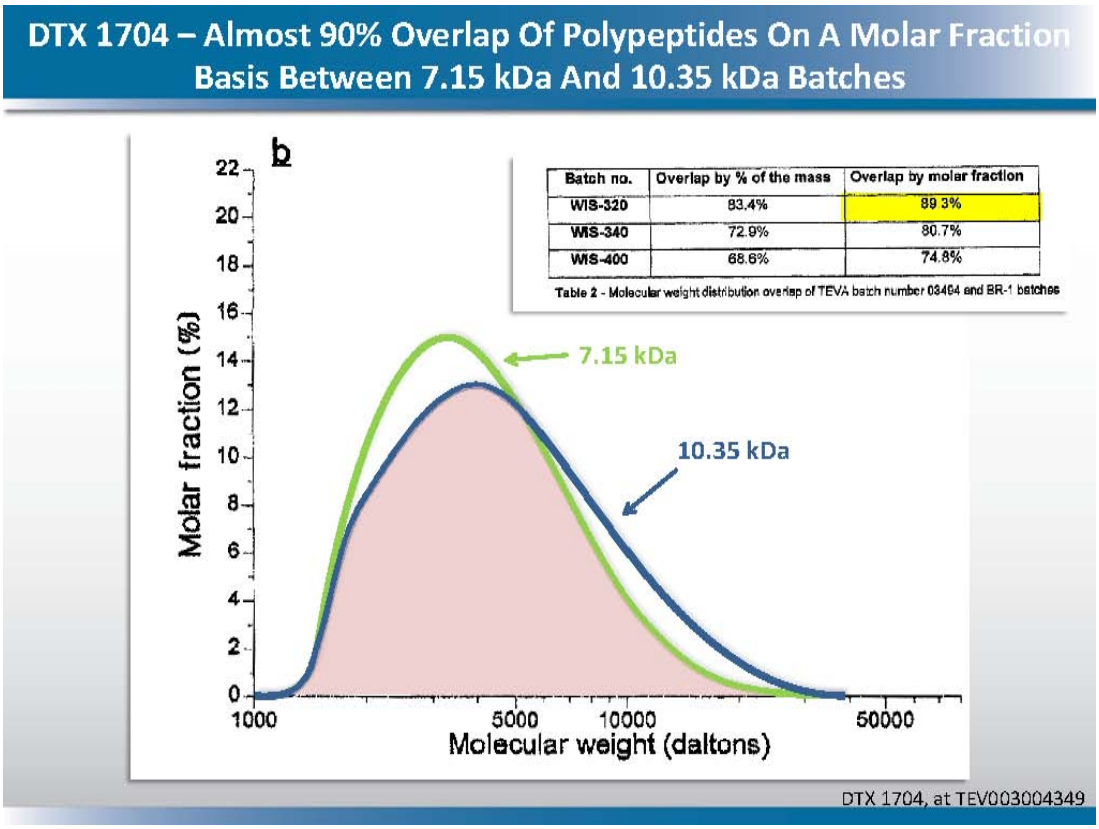
223. Referring to Figure 2 of the '808 patent, Dr. Zeiger testified that even batches of 7,150 daltons and 14,350 daltons, which differ in peak molecular weight by over 7 kDa, showed overlap by molar fraction of almost 75%. (Sept. Tr. 881:2-17, DTX-4030 at 14.)



224. In addition, Dr. Zeiger testified that the Teva batch at 7,150 daltons shows 80.7% overlap with a batch at 13,450 daltons. (Sept. Tr. 881:23-882:8; DTX-4030 at 15.)



225. When comparing copolymer-1 compositions with closer peak molecular weights, specifically 7,150 daltons and 10,350 daltons, he testified that there was even more overlap (89.3%) in the molecular weight profile. (Sept. Tr. 880:14-23; 882:10-14; DTX-4030 at 13, 16.)



226. Where the batches at 7,150 and 10,350 daltons already overlap by 89.3%, the overlap between batches of copolymer-1 at 9,000 and 10,000 daltons, with a difference of only 1 kDa, would be even more pronounced. (Sept. Tr. 881:14-22)

227. Dr. Zeiger testified that, due to the extensive overlap between batches of copolymer-1 at 7 kDa and 12 kDa, a person of skill in the art "would expect the continuity, the contiguousness of these products" to produce similar properties. (Sept. Tr. 875:25-876:5; 876:15-876:5; 905:13-21.) Because these two batches have an "overwhelming or an extremely large percent of sizes [of molecules] in common," and those molecules can be expected to "determine the overall properties, biological properties in a solution," Dr. Zeiger concluded that

the two batches would be expected to have similar biological properties. (Sept. Tr. 873:1-10; 875:25-876:5; 876:15-22.)

6. Teva Offered No Reliable Evidence Regarding Secondary Considerations of Nonobviousness

228. Teva has the burden to come forward with evidence showing secondary considerations of nonobviousness after the Defendants prove a prima facie case of obviousness. Secondary considerations of non-obviousness include (1) that the invention exhibits unexpected results; (2) that the invention satisfied a long-felt unmet need in the art; (3) the commercial success of the claimed invention; (4) the failure of others; and (5) copying of the claimed invention by others.

UNEXPECTED RESULTS

229. Teva did not come forth with evidence that its invention exhibited unexpected results. Teva presented no credible evidence at trial that the claimed ranges, no matter whether they are called "about 5 to 9 kilodaltons," "75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa," or any other variation, are "critical" to a showing of unexpectedly lower toxicity compared to the prior art.

230. In its pretrial brief, Teva stated that it would show that "[t]he claimed subject matter exhibits unexpected results - copolymer-1 within the claimed molecular weight range is active and less toxic than the prior art high molecular weight copolymer-1, and was shown to be effective in treating multiple sclerosis. To the extent Teva made any such showing, it demonstrated that it had a discovered these results in the window of "8000-12,000 by ultracentrifugation." (DTX 1200 at 1.) Because the '550 patent taught copolymer-1 with a weight average molecular weight of 10,000 daltons and greater," any alleged unexpected results were within the prior art.

231. When Teva filed the parent patent application for all of the patents-in-suit in May 1994, the Bornstein BR-1 study was finished and published in the *New England Journal of Medicine*. (PTX 31.) From that study, it was known that copolymer-1 was an active, effective treatment for multiple sclerosis. (Testimony of Irit Pinchasi; July Tr. 23:17-24:1; 268:23-269:1.) It was known one can "reduce inflammatory reactions at injection sites" by screening out batches of copolymer-1 with greater than 30% RBL degranulation. (PTX 31 at 409.) The copolymer-1 in that study was "not toxic in animals." (PTX 26 at 408.)

232. [redacted]

233. The analysis needed to determine whether the claimed copolymer-1 demonstrated unexpected results over the prior art, including the '550 patent, requires a comparison between the claimed ranges and the lower end of the '550 patent's range, namely the range between 10 and 13 kDa. Teva presented no toxicity data to the PTO regarding batches of copolymer-1 with reported average molecular weights between 8,400 and 13,000 daltons for the RBL test and no data whatsoever between 8,400 and 22,000 daltons for the mouse test.

234. Teva's fact and expert witnesses testified that, at best, Teva's toxicity data that was not given to the PTO shows "a trend" of lower toxicity with lower molecular weight. (See, e.g., July 11, 2011 Trial Tr. 59:24 - 60:24.) A "trend" does not show the required distinction of

where the claimed invention begins and the prior art leaves off. The admitted trial exhibits with RBL data show that, using Teva's purported 30% serotonin release cutoff for toxicity, there is no meaningful difference between the toxicity of batches above or below the 10 kDa cutoff in the prior art.

A LONG-FELT UNMET NEED IN THE ART

235. Teva did not come forth with evidence that its invention satisfied a long-felt, unmet need in the art. No one testified that there was a need for a copolymer-1 with lower molecular weight and reduced toxicity compared to the copolymer-1 described in the Bornstein BR-1 completed and published study.

COMMERCIAL SUCCESS

236. While Teva came forth with evidence that it sold billions of dollars worth of Copaxone, Teva presented no evidence that its success is attributable to what supposedly makes the claimed invention patentably distinct from the copolymer-1 used in the Bornstein BR-1 clinical trial. In fact, Dr. Green, Mylan's expert in the treatment of human patients for multiple sclerosis, confirmed that "no one in clinical practice" is aware of the lower molecular weight of the copolymer-1 marketed today, because the "numbers have changed on multiple occasions, so I think for a clinician, it's clinically irrelevant." (Sept. Tr. 1386:1-1388:21.)

237. In addition, Teva's product insert says that patients in the BR-1 study were given "COPAXONE." (PTX 697 § 14.1; Sept. Tr. 173:12-175:5.) If patients were already being administered "Copaxone" in the mid-1980s during the Bornstein BR-1 trials, Teva has failed to prove that the commercial success of "Copaxone" is attributable to features that changed between the time of the Bornstein BR-1 clinical studies and today.

THE FAILURE OF OTHERS

238. In its pretrial brief, Teva claimed that "[t]here were numerous failed efforts of others to develop effective and safe treatments for MS, including the failed attempts of a different pharmaceutical company, Repligen Corporation, to develop a copolymer-l drug product." Repligen Corporation is the assignee listed on the EP '620 Patent Application (DTX

1970.) There is no evidence in the record regarding Repligen's alleged efforts to do anything. The closest evidence was Dr. Grant being asked whether he knew of a product ever having been marketed that arose from the technology that's disclosed in the '620 EP publication. He said "no." Dr. Grant's ignorance does not amount to a showing by Teva that a company called Repligen tried and failed to make the claimed copolymer-1.

COPYING

239. Teva did not bring forth evidence suggesting that any alleged copying of the claimed invention proves that the patents-in-suit are not obvious. To the extent Teva argues that Sandoz has copied Teva's invention, that will be another example of Teva taking inconsistent positions in its regulatory strategy before the FDA and its patent strategy before the PTO and the courts. Teva is telling the FDA that Copaxone cannot be copied. (*See, e.g.*, DTX 1738 at TEV003009150 (Teva informing the FDA in its September 26, 2008 Citizen Petition that "the clinically active polypeptide sequences in Copaxone (glatiramer acetate injection) have not been sufficiently well defined to enable an ANDA or 505(b)(2) applicant to conclusively demonstrate that the clinically active polypeptide sequences in its purported generic product are qualitatively and quantitatively 'the same as' those in Copaxone").) Even if there were copying evidence, copying in the generic drug context is less probative of nonobviousness because applicants are required by the FDA to copy the reference listed drug to prove "sameness."

B. Conclusions of Law on Obviousness

240. A patent should not have issued and should be declared invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (2006). The party challenging validity has the burden of proof to show by clear and convincing evidence that

the claims are invalid. "[O]nce a challenger has presented a prima facie case of invalidity, the patentee has the burden of going forward with rebuttal evidence." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007).

241. A claimed invention is prima facie obvious over prior art references that disclose the same chemical composition in a range falling within and/or adjacent to the range recited in the claim. *See In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955)(noting the mere optimization or modification of one or more variables is generally unpatentable over the prior art, unless "the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art"); *In re Hill*, 284 F.2d 955, 959 (C.C.P.A. 1960) (holding obvious the "selection of lower reduction temperatures" over the prior art in the absence of unexpected results); *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782-83 (Fed. Cir. 1985) (claimed alloy reciting 0.3% molybdenum (Mo), 0.8% nickel (Ni) held obvious over prior art alloys reciting 0.25% Mo, 0.75% Ni and 0.31% Mo, 0.94% Ni, respectively); *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) ("Only if the results of optimizing a variable are unexpectedly good can a patent be obtained for the claimed critical range.") (quotations omitted).

242. "Where a claimed range overlaps with a range disclosed in the prior art, there is a presumption of obviousness." *Lazare Kaplan Int'l, Inc. v. Photoscribe Techs., Inc.*, 628 F.3d 1359, 1380–81 (Fed. Cir. 2010) (internal quotations and citations omitted); *see also Ormco Corp. v. Align Technology, Inc.*, 463 F. 3d 1299, 1311 (Fed. Cir. 2006); *Haynes Int'l, Inc. v. Jessop Steel Co.*, 8 F.3d 1573, 1577 n.3 (Fed. Cir. 1993) ("[W]hen the difference between the claimed invention and the prior art is the range or value of a particular variable, then a prima facie rejection is properly established when the difference in range or value is minor.").

243. To overcome the prima facie showing, the patent applicant has the burden to show that the newly claimed range was "critical" to some form of unexpected results, which in this case was purportedly unexpectedly reduced toxicity. *In re Aller*, 220 F.2d at 456 ("Such ranges are termed 'critical' ranges, and the applicant has the burden of proving such criticality," and even if proven, the invention "may still not be patentable if the modification was within the capabilities of one skilled in the art."). An applicant can also overcome a prima facie case by showing "(1) [t]hat the prior art taught away from the claimed invention; or (2) that there are new and unexpected results relative to the prior art." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004); see also *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) ("Once such a prima facie case is established, it falls to the applicant or patentee to rebut it, for example with a showing that the claimed [composition] has unexpected properties.").

244. "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *In re Peterson*, 315 F.3d 1325, 1328-30 (Fed. Cir. 2003) (*Id.* (citing *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." (citations omitted)).

245. The asserted claims of '808, '589, '847, '539, '098, '430, '476, and '161 patents are prima facie obvious because the molecular weight ranges described in the patents overlap or abut the disclosure in the '550 patent of a copolymer-1 composition with a minimum average molecular weight of 10 kDa.

246. The asserted claims of all patents-in-suit are prima facie obvious because the asserted claims describe an invention which is, at best, a mere optimization or modification of molecular weight ranges for copolymer-1, unless "the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art." *Id.*

247. "A nexus between the merits of the claimed invention and evidence of secondary considerations is required in order for the evidence [of secondary considerations] to be given substantial weight in an obviousness decision." *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 668 (Fed. Cir. 2000) (quoting *Simmons Fastener Corp. v. Illinois Tool Works, Inc*., 739 F.2d 1573, 1575 (Fed. Cir. 1984)); *see also Muniauction Inc. v. Thomson Corp*., 532 F.3d 1318, 1328 (Fed. Cir. 2008) ("Put another way, commercial success or other secondary considerations may presumptively be attributed to the patented invention only where the marketed product embodies the claimed features, and is coextensive with them.") (internal quotes omitted).

248. In the context of a generic drug litigation, a showing of copying is not compelling evidence of non-obviousness because the motivation to copy is often more related to regulatory concerns than an inability to design around a patent. *See, e.g., Eli Lilly and Co. v. Zenith Goldline Pharms., Inc.*, No. IP 99-38-C H/K, 2001 WL 1397304, at *14 (S.D. Ind. Oct. 29, 2001) ("[T]he ANDA procedures established by the Hatch-Waxman Act require generic drug manufacturers to copy the approved drug. Variations undermine the FDA's ability to assume that if the patented drug is safe and effective, the generic competitor will also be safe and effective."); *Santarus, Inc. v. Par Pharm., Inc*., 720 F. Supp. 2d 427, 458 (D. Del. 2010) ("Thus, even assuming Par's conduct in reverse engineering Zegerid amounted to 'copying' of the patents-in-suit, such conduct is not persuasive objective evidence of non-obviousness."); *Purdue*

Pharma Products L.P. v. Par Pharm., Inc., 642 F. Supp. 2d 329, 373-74 (D. Del. 2009) ("[A] showing of copying, which Plaintiffs have provided here, . . . is not compelling evidence of non-obviousness in the Hatch-Waxman context."), *affd.*, 377 Fed. Appx. 978 (2010); *In re GPAC, Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) ("[M]ore than the mere fact of copying by an accused infringer is needed to make that action significant to a determination of the obviousness issue.") (internal quotations omitted).

249. Teva did not overcome the prima facie showing of obviousness because it did not show a new and unexpected result which is different in kind and not merely in degree from the results of the prior art.

C. Teva Is Judicially Estopped From Presenting a Position at Trial That Is Inconsistent With Its Prior Arguments to the PTO

The '550 patent discloses copolymer-1 with a minimum average molecular weight in excess of 10,000 daltons. (PTX 26, '550 patent, col. 1:57-65 ("The novel compositions of matter according to the present invention, to be used for the treatment of EAE, and for obtaining protection against this autoimmune disease, comprises a synthetic water-soluble copolymer consisting of a plurality of amino acids, the molecular weight of the copolymer being in excess of 10,000 and preferably above about 18,000. . . .").) Even if the evidence did not support a finding that the '550 patent discloses a copolymer-1 composition with a molecular weight of 10,000 daltons, the Court should make the following findings of fact and hold that Teva is judicially estopped from arguing that the '550 patent does not disclose a copolymer-1 composition with a minimum average molecular weight of 10,000 daltons (10 kDa).

1. Findings of Fact on Judicial Estoppel

250. During prosecution of the patents-in-suit, the PTO rejected Teva's asserted claims as anticipated by the '550 patent. (PTX-17 TEV000304219.) In its rejection, the PTO stated that

the '550 patent "disclose[s] treating multiple sclerosis (column 1, line 30) with copolymer-l having a molecular weight of more than 10,000 (column 1, line 62) but not more than 25,000 (see the fourth line of claim 1). When near the lower limit (10,000), the molecular weight limitations of instant claims 17-19 would clearly be met." (*Id.*)

251. In response, Teva repeatedly argued to the PTO that the '550 patent was different than its present invention because the '550 patent describes copolymer-1 with a minimum average molecular weight of 10 kDa. (PTX-17 at TEV000304384.)

252. Based on Teva's argument, the PTO withdrew its rejections. (*Id.* at TEV000304389.)

253. Teva's Dr. Grant has now testified that the '550 patent does not disclose a copolymer-1 with a minimum average molecular weight of 10 kDa. (Sept. Tr. 1482:16-20, 1483:17-24.)

2. Conclusions of Law on Judicial Estoppel

254. Judicial estoppel is an equitable doctrine that serves to protect the "integrity of the judicial process" by "prohibiting parties from deliberately changing positions according to the exigencies of the moment." *New Hampshire v. Maine*, 532 U.S. 742, 749-50 (2001) (internal citations omitted).

255. As articulated by the Supreme Court, judicial estoppel will be found when: (1) a party's later position is "clearly inconsistent" with its earlier position, (2) judicial acceptance of an inconsistent position in a later proceeding would create a perception that either the first or the second tribunal was misled, and (3) the party seeking to assert the inconsistent position would derive an unfair advantage or impose an unfair detriment on the opposing party if not estopped. *Id.* at 750–51.

256. When determining the issue of judicial estoppel, the Federal Circuit looks to the law of the regional circuit. *See Water Technologies Corp. v. Calco, Ltd.*, 850 F.2d 660, 665 n.3 (Fed. Cir. 1988).

257. In the Second Circuit, a party seeking to apply judicial estoppel must show both that its opponent has taken an inconsistent position and that a court in an earlier proceeding has adopted this position. *See Uzdavines v. Weeks Marine, Inc.*, 418 F.3d 138, 148 (2d. Cir. 2005), citing *Stichting v. Schreiber*, 407 F.3d 34, 45 (2d Cir. 2005).

258. Judicial estoppel may be applied even when the proceedings involve an administrative agency, such as the PTO, and a court, as opposed to two courts. *See Simon v. Safelite Glass Corp.*, 128 F.3d 68, 72 (2d. Cir. 1997) ("Numerous decisions have approved the application of judicial estoppel where the prior statements were made in administrative or quasi-judicial proceedings."). The Second Circuit has emphasized that "[a]scertaining the truth is as important in an administrative inquiry as in judicial proceedings," because, the court explains, "[a] growing number of disputes are adjudicated before administrative agencies and tribunals, and those proceedings often form the factual record for later appeals to a judicial court." *Id.* at 72.

259. Where an applicant makes representations to the PTO that result in the issuance of a patent, the applicant may be judicially estopped from taking an inconsistent position in a later proceeding. *See, e.g.,Yeda Research & Devel. Co. Ltd. v. Imclone Systems Inc.*, 443 F.Supp. 2d 570, 623-624 (S.D.N.Y. 2006). In *Yeda Research & Devel. Co.*, the defendants represented to the PTO during prosecution that a research paper by two of the inventors disclosed a particular claim element, in order to prove conception. *Id.* at 623. The PTO accepted their argument, and the claims were allowed. *Id.* In subsequent litigation, the defendants attempted to argue that the

inventors' paper *did not* disclose the claim element. *Id.* The court held that "[t]he doctrine of judicial estoppel squarely applies to the arguments now advanced by defendants." *Id.* Because the defendants had gained the benefit of their initial argument by virtue of obtaining the patent, the court concluded, "we will not permit defendants to argue now that their assertions to the PTO were incorrect." *Id.* at 624.

260. All of the elements for application of judicial estoppel are met in this case.

261. First, through its expert Dr. Grant, Teva is now taking a clearly inconsistent position from the statements it previously made to the PTO. During prosecution of the patents, Teva stated that its asserted claims were different from the '550 patent because it disclosed copolymer-1 with a minimum average molecular weight of 10 kDa, whereas now, Teva's expert has testified that the '550 patent in fact *does not* disclose copolymer-1 with a molecular weight of 10 kDa.

262. Second, Teva received a favorable decision from the PTO—allowance of its asserted claims—as a result of its representations that the '550 patent describes copolymer-1 with a minimum average molecular weight of 10 kDa. *See Yeda Research & Devel Co.*, 443 F.Supp. 2d at 623-624.

263. Third, Teva would derive an unfair advantage from being allowed to represent its invention in an inconsistent way in two different proceedings according to the "exigency of the moment." *New Hampshire v. Maine*, 532 U.S. at 749-50.

264. Teva is therefore estopped from asserting at trial a position that is inconsistent with its prior statements to the PTO.

V. THE ASSERTED PATENTS ARE UNENFORCEABLE DUE TO INEQUITABLE CONDUCT

A. Findings of Fact: Dr. Pinchasi Intentionally Deceived the PTO by Presenting a False Black and White Relationship Between Molecular Weight and Toxicity

1. Dr. Pinchasi Selected the Data That Became Example 2

265. Teva relied on a difference in molecular weight from the prior art to obtain all nine of the patents-in-suit. Two of the patents contain a range of 5 to 9 kDa, two "about 4 to about 9 kDa" and four with "75% between 2 and 20 kDa."[3] The prior art '550 patent claimed copolymer-1 in a molecular weight range of "in excess of 10 kDa," and the prior art EP '620 patent discloses copolymer-1 in a range of 5 to 50 kDa.

266. Dr. Pinchasi selected the data that became Example 2, which purported to show that lower molecular weight copolymer-1 results in lower levels of toxicity. (July Tr. 204:12-18.) Example 2 is contained in all nine of the patents-in-suit.

[3] While the '898 patent claims do not contain express numerical limitations, Dr. Pinchasi's conduct with respect to this patent is the same, and as with all the other patents, Teva relied on the particular molecular weights in the prior art during prosecution of the '898 patent to distinguish its claims from the prior art. Specifically, even though the proposed claims of the application that led to the '898 patent had no express numerical limitations for molecular weight, the PTO rejected the claims as anticipated by the '550 patent. (PTX 15 at TEV000309098-99; TEV000309109.) Teva argued that the rejection was improper because "[t]he cited reference [the '550 patent] teaches a minimum molecular weight of 10 kilodaltons. In contrast, the presently-claimed invention relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range of about 2 kDa to about 20 kDa and having an average molecular weight of about 4 kDa to about 8.6 kDa. (*Id.* at TEV000309118.) With these representations on the record, the Examiner eventually allowed the claims of the '898 patent. Thus, if the Court finds the other patents unenforceable due to Dr. Pinchasi's inequitable conduct, it should also find the '898 patent unenforceable.

267. Example 2 provided the PTO with RBL or mouse death results from only six different batches of copolymer-1:

Average Molecular Weight	RBL Result	Mouse Result	% of species with M.W. over 40 kDa
6,250	**Less toxic**	**Not shown**	**<2.5**
7,300	**Less toxic**	**Non-toxic**	**<2.5**
8,400	**Not shown**	**Non-toxic**	**Not shown**
13,000	**More toxic**	**Not shown**	**>5**
14,500	**More toxic**	**Not shown**	**>5**
22,000	**Not shown**	**Toxic**	**Not shown**

(PTX 1, Example 2.)

268. The patents do not disclose toxicity data for batches of copolymer-1 having average molecular weights between 8,400 and 13,000 daltons, and particularly, do not contain toxicity data for batches of copolymer-1 having average molecular weights between 10,000 and 13,000 daltons.

269. Dr. Pinchasi selected the Example 2 data from a voluminous amount of data available to her that was not presented in the patents-in-suit. (July Tr. 203:23-204:7; 206:20-24.) Dr. Pinchasi signed and approved a formal Teva RBL specification in 1989 indicating that toxicity data from at least 50 batches was available. (DTX 999A at TEV001222392-RC.) Despite knowing of the large amounts of data available, she chose to include toxicity data for only the four batches of copolymer-1 in the patent application. (July Tr. 207:10-14.)

270. Dr. Kimber is currently Chairman of the Department of Toxicology at the University of Manchester. (July Tr. 367:6-8.)

271. Previously, he was Principal Fellow and Head of Research at Syngenta Central Toxicology Laboratory in Macclesfield, England. (July Tr. 367:18-22, 368:5-10; DTX 1321.) At Syngenta, Dr. Kimber's research covered immunology and toxicology, with a particular focus on the regulation of immune responses and allergic disease. (July Tr. 368:17-20.)

272. Dr. Kimber received both his Masters of Science and his Ph.D. from the University of Manchester. (July Tr. 368:24-369:1; DTX 1321.)

273. Since the early 1990s, he has served on advisory boards and industry panels for such organizations as the United Kingdom's Medical Research Council and Ministry of Defence, as well as the World Health Organization, with a particular emphasis on immunotoxicology issues. (July Tr. 370:11-21; DTX 1321.)

274. Dr. Kimber serves on advisory panels for Procter & Gamble, PepsiCo Europe, Roche Pharmaceuticals, and AstraZeneca Pharmaceuticals. (July Tr. 370:6-10.) He also serves on the editorial boards of several peer-reviewed publications, such as the "Journal of Immunotoxicology and Journal of Immunology." (July Tr. 370:22-371:8.)

275. Dr. Kimber has written or co-authored over 650 publications, including 450 peer-reviewed articles and over 100 book chapters. (July Tr. 369:16-20; DTX 1321) He was recently awarded the OBE, or Officer of the Order of the British Empire, for services to science. (July Tr. 371:17-24.)

276. Dr. Kimber testified that a person of skill in the art would have understood from the description of four copolymer-1 batches in the RBL testing section of the patents that only four batches were tested, and would not have understood that Teva had data for many more batches from the same body of evidence. (July Tr. 401:16 – 402:3)

277. The data available to Dr. Pinchasi also included the data table found in Mr. Nachshen's patent file. A color-coded version showing data that was selected (green boxes) and not selected (orange boxes) is reproduced below:

Batch Number	Average Molecular Weight	Peak III Select	% Release from RBL	Safety *In vivo*	Skin Irritation
123-094	6250	41.0	12.4	0/5	N.T.
123-090	7300	43.3	21	0/5	14±2.5 (14±1.2]
123-095	8400	40.3	25.6	0/5	11.6±1.5(12±1.2]
04792	9250	43.9	31.3	0/5	13.8±1(14±1.2]
04892	9600	44.2	50.5 (?)	0/5	N.T.
04992	9900	43.9	51.5 (?)	0/5	13.8±1.2(14±1.2]
123-096	10,950	44.2	39.8	0/5	N.T.
04592	11,050	45.3	41.3	0/5	16+1.2(16.4+0.8)
04692	11,900	45.8	41.7	0/5	N.T.
04492	12,150	47	47.6	0/5	18±1.8(17.2 + 1)
196/2	13,000	45.7	66.9	0/5	16.2±1[17 + 1.55]
196/1	14,500	44.66	67.8	0/5	15.6±0.8(14.8+1)
186/1	22,000	47.27	60.3	3/5	N.T.

(DTX 999A at TEV00122355-RC.)

278. Dr. Pinchasi was the only person working on the night the patent application was submitted who had an overall knowledge of the biological data, and she was the only one who could have selected the data. (July Tr. 11:6-12; 143:19-22, 165:10-18) Dr. Pinchasi claims she did not actually select the data, and only provided it to Dr. Haber for inclusion in the patent application. But Haber had no more than a superficial understanding of the toxicity data. (July Tr. 145:12-22; DTX 1389 at 28:25-29:6 (Haber).) Similar, Neil Nachshen, the self-described "scribe" of the patent application, testified that before that evening, he had "no previous knowledge or experience of working with this molecule at all." (DTX 1394 at 22:2-18 (Nachshen).)

279. Dr. Pinchasi repeatedly confirmed that, after providing the data, she reviewed the application to make sure it was "in line" with what she knew, and was "accurate" from her perspective. (July Tr. 205:9-21.) Dr. Pinchasi was also responsible for final approval of the patent application. (July Tr. 213:12-16.)

280. Teva did not submit any additional toxicity data during prosecution of the patents-in-suit to supplement the limited toxicity data in the patent application. (July Tr. 516:24-518:6 (Rzucidlo).)

2. Dr. Pinchasi Intentionally Deceived the PTO by Selectively Presenting Only the Favorable Mouse Test Data

281. There are only three mouse death data points provided in Example 2 of the patents. (PTX 1, 808 patent, col. 3:23-45.) Molecular weights of 7,300 and 8,400 daltons produced no mouse deaths, while 22,000 daltons, in the range of the prior art, produced three mouse deaths. (*Id*.) Teva and Dr. Pinchasi knew that the 13,000 and 14,500 dalton batches, represented as part of the RBL data in Example 2, produced no mouse deaths, and this data was not disclosed to the PTO. (DTX 3149; July Tr. 149:16-150:21 (Pinchasi).) Teva and Dr. Pinchasi also knew that copolymer-1 batches with molecular weights of 9,900, 10,950, 11,050, 11,900, and 12,150 daltons produced no mouse deaths. (*Id.*) Toxicity data for these batches were also kept from the PTO.

282. Dr. Pinchasi was aware that the copolymer-1 batches having molecular weights between 8,400 and 22,000 daltons did not cause mouse deaths, as the information came from her files, and the summary table has her handwriting on it. (July Tr. 123:5-9.)

283. Teva did not offer any evidence of mistake, inadvertence, or negligence in the selection of the mouse data it provided to the PTO on May 24, 1994. The single most reasonable inference able to be drawn from this evidence is that Dr. Pinchasi acted with a specific intent to

deceive the PTO. By withholding any data points between 8.4 kDa and 22 kDa, the PTO could not make an informed decision whether the *in vivo* mouse test showed unexpectedly low toxicity in the claimed range over the prior art.

3. Dr. Pinchasi Intentionally Deceived the PTO by Presenting Only the RBL Test Data that Supported Teva's Patentability Proposition

284. Example 2 contains RBL histamine release data for only four batches of copolymer-1. (PTX 1, Example 2.) The selected data showed less than 30% degranulation for batches at 6,250 and 7,300 daltons, and more than 60% degranulation for batches at 13,000 and 14,500 daltons. (PTX 1, '808 Patent, col. 4:16-24.)

285. Dr. Pinchasi admitted that all of Teva's RBL data indicated to her that there was only a trend or probability of lower toxicity, expressed as RBL degranulation of less than 30%, at lower molecular weights. (July Tr. 246:5-18, 262:7-14.) Dr. Pinchasi testified that copolymer-1 batches with average molecular weights of 7,000 – 10,000 daltons had only a 50% chance of being non-toxic. (July Tr. 257:23-258:9.) Drs. Kimber and Baird agreed that the data provided in Example 2 suggests two "camps" with clear differences, and not merely a trend or probability of lower toxicity at lower molecular weights and vice versa. (July Tr. 401:7-15 (Kimber); July Tr. 601:5-12 (Baird).) Dr. Baird also confirmed that no RBL data between 7,300 daltons and 13,000 daltons was provided to the PTO. (July Tr. 665:19-666:8.)

286. Dr. Pinchasi admitted that the concept of a "trend" or "probability" of lower toxicity at lower molecular weights was nowhere in the patent application. (July Tr. 262:12-20.) Both Dr. Kimber and Dr. Baird testified that the data in the patent does not indicate merely a trend towards increased toxicity. (July Tr. 401:7-15 (Kimber); July Tr. 601:5-12 (Baird).) Both experts agreed, based upon a review of a portion of Teva's toxicity data, that the toxicity data for other copolymer-1 batches not shown in the patent did not show a clear demarcation in toxicity

above and below 9,000 daltons. (July Tr. 601:13-24; 605:9-18 (Baird); 404:18-406:5 (Kimber).) In contrast, only the black and white picture presented in Example 2 was provided to the PTO. Teva characterized the difference in toxicity in Example 2 as distinct from the prior art and unexpected, not as merely a "trend." (PTX 13 at TEV000304151-152; PTX 17 at TEV000304385; PTX 18 at TEV000310450-51; PTX 19 at TEV000304498).

287. While the patents only contained RBL data for four copolymer-1 batches, Teva possessed data for numerous copolymer-1 batches that were inconsistent with the data in the patents. Dr. Pinchasi agreed that she knew of many individual data points that are inconsistent with the data in the patent application. (July Tr. 245:17 – 246:4) She testified that a number of batches with molecular weights of around 6,250 and 7,300 daltons were toxic using the RBL test. (DTX 3059; PTX 43T; July Tr. 238:2-239:11, 244:7-245:11, 245:17-246:4) She also testified that batches having molecular weights around 13,000 and 14,500 were non-toxic using the RBL test. (DTX 3477; July Tr. 253:12 – 257:4)

288. Dr. Baird testified that she would want to see all the data to make an interpretation. (July Tr. 650:19-652:16; 685:22-687:7 (Baird))

289. [redacted]

290. [redacted]

[redacted]

[4] The differences from these data and the data presented at closing are due to deletion of arguably duplicate RBL measurements. Because data showing the same RBL values for the same batch may be one measurement written twice in two separate documents, to be conservative, potentially duplicate RBL measurements for the same copolymer-1 batches have been deleted, resulting in a less than 1% difference in the percentage of non-toxic batches with a molecular weight range between 10,000 and 13,000 kDa and a less than 2% difference in the percentage of non-toxic batches with a molecular weight range between 7,000 and 9,999 kDa. The conclusion remains unchanged. There is no meaningful difference in toxicity when comparing batches of copolymer-1 just above and below 10 kDa.

292. Teva did not offer any evidence of mistake, inadvertence, or negligence in the selection of the RBL data it provided to the PTO on May 24, 1994. The single most reasonable inference able to be drawn from this evidence is that Dr. Pinchasi acted with a specific intent to deceive the PTO. By withholding any data points between 7.3 kDa and 13 kDa, the PTO could not make an informed decision whether the *in vitro* RBL test showed unexpectedly low toxicity in the claimed range over the prior art.

4. Dr. Pinchasi Intentionally Deceived the PTO by Describing its RBL Test as Reproducible When She Knew The Opposite Was True

293. By 1989, Dr. Pinchasi knew Teva's RBL test suffered from large inter-assay and intra-assay variability, as well as inconsistent reproducibility. (July Tr. 211:15-212:12.) For example, Dr. Pinchasi testified that a batch which tested at 40% degranulation one day could test at 53% degranulation the next. (July Tr. 212:9-12.) Dr. Pinchasi also knew in 1989 that the RBL degranulation test was not controllable. (July Tr. 212:21-25.)

294. In its 1994 application, Dr. Pinchasi included general information about its RBL test that was taken from a 1988 memorandum, and ignored her signed, 1989 approved formal RBL specification that described Teva's experience with the RBL test as having inconsistent reproducibility and a lack of controllability:

> It is clear from this table that the RBL system is inconsistent in its reproducibility, and both inter-assay and intra-assay large variations were observed…We thus feel that this assay can not be properly controlled.

(DTX 999A at TEV001222393-394-RC; DTX 1146 at TEV000881293-294, TEV000881362-370 (showing 1988); July Tr. 155:3-19, 213:1-16.) This formal specification is contained within Teva's patent file for the patents in suit. (*See* DTX 999A at TEV001222392-396-RC.)

Dr. Pinchasi testified that as of May 1994, her beliefs about the RBL test's reproducibility and unacceptability as a quality control test had not changed. (July Tr. 213:1-3.)

295. Dr. Kimber agreed with Dr. Pinchasi's interpretation and characterization of the RBL data in DTX 999A at TEV001222392-396. (July Tr. 397:7-11.)

296. The 1989 document contains RBL data for 10 batches of copolymer-1. The molecular weights of these batches in the 1989 document are found in PTX 43T and PTX 34T:

Batch Number	Molecular Weight
RE-6481	**6800 daltons (PTX 43T at YED000003029)**
27-J-8	**13,500 daltons (PTX 43T at YED000003028)**
31-B	**8500 daltons (PTX 43T at YED000003029)**
31-G-1	**6400 daltons (PTX 43T at YED000003028)**
32-D-3	**6900 daltons (PTX 43T at YED000003028)**
30-D-3	**6300 daltons (PTX 43T at YED000003028)**
BY-37	**15,000 daltons (PTX 43T at YED000003029)**
24M	**9200 daltons (PTX 34T at YED000002945)**
RE-6385	**7200 daltons (PTX 43T at YED000003029).**
31-G	**6400 daltons (PTX 43T at YED000003028)**

(DTX 999A at TEV001222396-RC.)

297. The table on TEV001222396 contains 43 different RBL degranulation values for the eight of these ten batches that have molecular weights between 5,000 and 13,000 daltons. As summarized below, the large majority of these batches had RBL values above 30%, and would have been classified as "toxic" batches using a 30% degranulation cutoff. All of the batches with molecular weights between 7,000 and 9,000 daltons and between 9,000 and 13,000 daltons

would have been classified as "toxic" batches based upon the RBL degranulation results and over 80% of the batches with molecular weights between 5,000 and 9,000 daltons would have been classified as "toxic":

Molecular weight range (daltons)	Number of batches	% non-toxic batches at a 30% cut-off	% toxic batches at a 30% cut-off
5,000 – 9,000	**37**	**18.9%**	**81.1%**
7,000 – 9,000	**6**	**0%**	**100%**
9,001 – 13,000	**6**	**0%**	**100%**

298. Dr. Pinchasi reviewed and approved the patent application, which represented that "[t]he Rat Basophilic Leukemia cell line (RBL-2H3) was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system." (PTX 1 at 3:50-53; July Tr. 210:2-6) But she admitted that, in May 1994, Teva knew the RBL test was not reproducible, and that it was "very problematic" as a formal quality control test. (July Tr. 210:12-18.) Despite knowing the flaws of the RBL assay when applied to copolymer-1, and despite having the data at hand showing that only 18.9% of batches having an average molecular weight between 5,000 and 9,000 daltons were non-toxic using the RBL test, Dr. Pinchasi chose to describe the RBL assay as being reproducible in the patents-in-suit. (July Tr. 210:12-25.)

299. Teva did not offer any evidence of mistake, inadvertence, or negligence for its decision to describe the RBL test as reproducible when it knew that, in the context of copolymer-1, the test was flawed. The single most reasonable inference able to be drawn from this evidence is that Dr. Pinchasi acted with a specific intent to deceive the PTO. By withholding the

reliability of the RBL test from the Examiner, Dr. Pinchasi limited the Examiner's ability to assess the evidence of unexpected results.

5. Dr. Pinchasi Intentionally Deceived the PTO by Describing a Relationship Between Teva's RBL Test and Human Side Effects That Had Not Been Observed

300. Dr. Pinchasi represented to the PTO that Teva's RBL test could be used to screen copolymer-1 for clinical applications, and the patent clearly stated that the RBL test is useful to screen for "undesirable local and/or systemic side effects." (DTX999A; PTX 1, col. 3:63-67.) But Dr. Pinchasi knew in May, 1994, and admits that she continued to believe in 2003 and 2004, and at trial, that there was no evidence of any correlation between RBL and side effects in humans. (July Tr. 267:11-268:5.)

301. Dr. Kimber agreed with Dr. Pinchasi's assessment, and he was not aware of any correlation between RBL and side effects in humans. (July Tr. 417:9-17.) He noted that the Bornstein study is inconsistent with a correlation between RBL degranulation and side effects. (July Tr. 417:18-418:13.) The Bornstein study used 14,000-23,000 dalton batches of copolymer-1 having less than 30% degranulation levels, and noted a high prevalence of injection site reactions. (PTX 31.) Dr. Kimber testified that if low RBL levels were correlated with low levels of side effects, the Bornstein trial should not have had such high levels of side effects. (July Tr. 418:8-13.)

302. Teva did not offer any evidence of mistake, inadvertence, or negligence for its decision to falsely state the RBL test could be used to screen copolymer-1 for clinical applications even though there was no evidence of any correlation between RBL and side effects in humans. The single most reasonable inference able to be drawn from this evidence is that Dr. Pinchasi acted with a specific intent to deceive the PTO. By withholding the usefulness of the

RBL test from the Examiner, Dr. Pinchasi limited the Examiner's ability to assess the evidence of unexpected results.

6. Dr. Pinchasi Simultaneously Gave the PTO and the FDA Opposite Descriptions of Teva's "New" Copolymer-1

303. Dr. Pinchasi coordinated all of Teva's contact with the FDA regarding copolymer-1. (July Tr. 268:3-5.) Dr. Pinchasi admitted that Teva purposely employed a strategy of trying to convince the FDA that the higher molecular weight copolymer-1 Teva had used in its BR-1 (Bornstein) clinical trial was comparable to the lower molecular weight copolymer-1 used in the Johnson clinical trial. (July Tr. 269:3-6, 270:2-6.) Teva told the FDA that the BR-1 batches had a comparable molecular weight distribution to lower molecular weight copolymer-1. (DTX 1023 at TEV000000490; July Tr. 269:22-270:6.) Dr. Pinchasi admitted that Teva had to tell the FDA that the high molecular weight BR-1 material and Copaxone were equivalent in order to obtain FDA approval for Copaxone. (July Tr. 42:25-43:20; 269:6 – 270:6.)

304. Three of the four inventors of the patents-in-suit (Drs. Teitelbaum, Arnon, and Sela) were co-authors with Dr. Bornstein on the 1987 *New England Journal of Medicine* article reporting the results of the BR-1 Bornstein clinical trial. (PTX 31.) [redacted]

[redacted]

305. Teva set out and successfully convinced the FDA that the higher molecular weight copolymer-1 in the Bornstein BR-1 study was comparable to the lower molecular weight copolymer-1 for which Teva sought FDA approval. (July Tr. 268:24-270:7 (Pinchasi).) [redacted]

306. At the same time, Teva told the PTO the opposite: that lower molecular weight copolymer-1 was preferable to copolymer-1 at higher molecular weights because it produced more favorable toxicity outcomes. (PTX 1, '808 patent, col. 2:20-3:27, Example 2 ("Toxicity Analysis").) Teva continued to argue that it had demonstrated lower toxicity throughout the prosecution of the patents-in-suit. (*E.g.*, PTX 1, '808 patent; col. 5:9-6:3 ("Preparation of low-toxicity copolymer-1"); PTX 19 at TEV000301498 ("The Examiner states that it would have been obvious to determine optimal values within a disclosed range. The claimed range, however, shows unexpected results. As shown in Example 2, for instance, the claimed peptides have unexpectedly low toxicity").)

307. In its original NDA submission, Teva sought approval to set the specification for average molecular weight of copolymer-1 at 4,700 to 13,000 daltons. (July Tr. 85:23-86:3.)

7. Dr. Pinchasi's Testimony and Conduct Lacks Credibility

308. At trial Dr. Pinchasi attempted to place responsibility for the patent application away from herself and with Dr. Haber. (July Tr. 116:15-20, 145:12-22, 147:8-19.) But Dr. Haber and Nachshen testified that Dr. Pinchasi was the person responsible for the copolymer-1 project at Teva and for the meeting on preparing the application. (DTX 1389 at 47:23-48:07,

51:14-19, 55:22-56:09 (Haber); DTX 1394 at 27:2-20, 28:3-12 (Nachshen); *see also* July Tr. 11:6-12.) As detailed previously, Dr. Pinchasi was the only person working on the night the patent application was submitted who had an overall knowledge of the biological data, and she was the only one who could have selected the data. (July Tr. 11:6-12; 143:19-22, 165:10-18.)

309. When preparing the patent application, Dr. Pinchasi knew "you can get quite different molecular-weight results depending on the method." (July Tr. 254:18-25, 277:13-23.) In particular, Dr. Pinchasi was aware that the molecular weights within her "optimum range" of 6000-9000 actually "corresponded" to 8000 to 12,000 molecular weights measured by ultracentrifugation (DTX 1200), placing this "optimum range" within the '550 prior art range of 10,000 and above. Dr. Pinchasi chose not to inform the Patent and Trademark Office of that fact. (July Tr. 192:6-193:1.)

310. Even after "it became apparent that there is no such clear-cut difference" in human side effects between higher molecular weight copolymer-1 and the claimed lower molecular weight copolymer-1 (July Tr. 266:18-25), Dr. Pinchasi chose not to inform the Patent and Trademark Office of that fact, either.

311. At trial, Dr. Pinchasi claimed to have had a discussion with the FDA about the probability of toxic effects as molecular weight increased. (July Tr. 270:21-271:2.) However, at her deposition, Dr. Pinchasi had unequivocally testified that she did not recall such a discussion with FDA. (July Tr. 271:8-17.) No document or other witness corroborated Dr. Pinchasi's new testimony at trial. (July Tr. 271:25-272:9.)

312. To the contrary, the record establishes that Dr. Pinchasi told the FDA that the higher-molecular-weight copolymer-1 in the BR-1 study was comparable to the copolymer-1 lower molecular weight at Teva. (July Tr. 269:7-270:7; 274:8-15.)

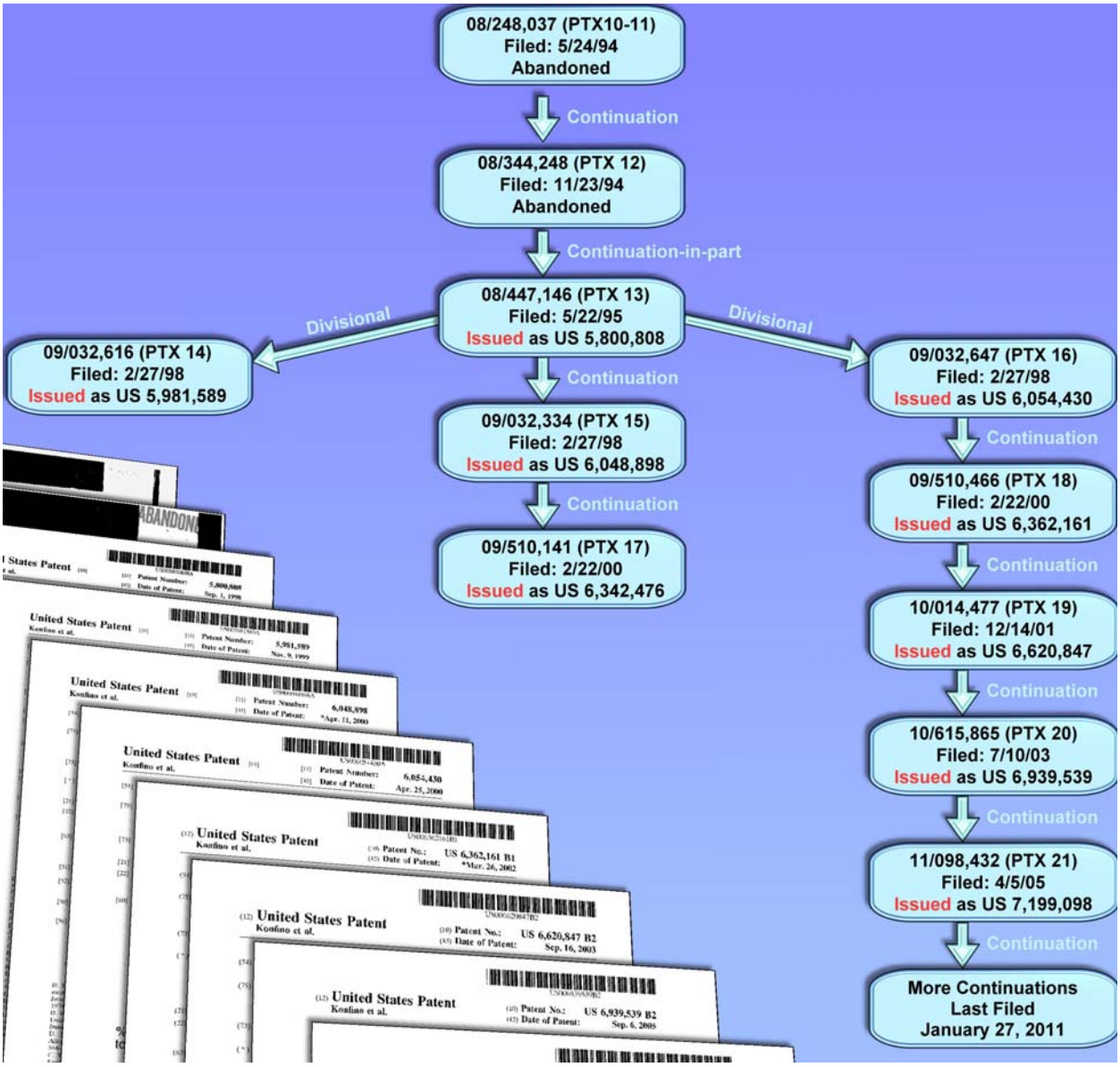
8. But For The Omission of the Relevant Data, the Claims of the Patents-in-Suit Would Not Have Issued

313. All nine patents-in-suit stem from a patent application filed on May 24, 1994. (PTX 10.) The original title of the invention was "Coplymer-1 Improvements in Compositions of Copolymers." (PTX 10 at TEV003009929.) The "improvement" related to the alleged reduced toxicity compared to the prior art. The Background of the Invention section defines "copolymer-1" and cites the '550 patent for the proposition that copolymer-1 has an average molecular weight of 23,000 daltons. (*Id.*) Example 2, entitled "Toxicity Analysis," sets forth an *in vivo* mouse toxicity test in which batches of copolymer-1 with average molecular weights of 7.3 and 8.4 kilodaltons were "non-toxic," whereas the prior art copolymer-1 with an average molecular weight of 22 kilodaltons was "toxic." (*Id*. at TEV003009932-34.) Example 2 also includes information from an *in vitro* RBL toxicity test, comparing batches of copolymer-1 with low average molecular weights of 6.25 kDa and 7.3 kDa to prior art batches of copolymer-1 with higher average molecular weights of 13 and 14.5 kDa.

314. Mr. Eugene C. Rzucidlo provided the Court an overview of the prosecution history of the patents-in-suit. Mr. Rzucidlo obtained his Bachelor of Science in Chemistry degree in 1963. He taught courses in chemistry and later worked as a research chemist until 1970. (July Tr. 496:19-497:24.) In 1970, he became a patent examiner at the PTO; and after four years, he became a primary patent examiner. (July Tr. 497:25-498:10.) Mr. Rzucidlo worked in PTO Art Group 140, which was responsible for examining patent applications related to polymers. (July Tr. 498:14-17.) He later became a member of the Board of Patent Appeals, serving in that position until he left the PTO in 1985. (July Tr. 498:24-499:8.) He has practiced before the PTO continuously since 1985. (July Tr. 499:16-500:11.)

315. Mr. Rzucidlo testified that examiners are generally responsible for determining whether a patent application satisfies the statutory requirements such as novelty and nonobviousness. (July Tr. 501:23- 502:11.) He also testified that examiners rely upon the Manual of Patent Examining Procedure for guidance when examining applications. (July Tr. 501:23- 502:11.) For example, Mr. Rzucidlo testified that the MPEP provides examiners specific guidance regarding claims with numerical ranges. (July Tr. 502:12-503:17.)

316. Mr. Rzucidlo created the following chart depicting the relationship among the applications that led to the nine patents-in-suit.



317. All nine patents-in-suit share PTX 11, 12, and 13 as parent applications. The applications in PTX 13 and PTX 14, which issued as U.S. Patent No. 5,800,808 ("the '808 patent") and No. 5,981,589 ("the '589 patent"), respectively, are especially closely related applications because their claims are identical except that the '808 patent claims "a method of manufacturing copolymer-1 . . . having a molecular weight of about 5 to 9 kilodaltons," whereas the '589 patent clams "copolymer-1 having a molecular weight of about 5 to 9 kilodaltons" made

by the same method as in claim 1 of the '808 patent. (*Compare* PTX 1, claim 1, *with* PTX 2, claim 1; *see also* PTX 14 at TEV000309013.) In other words, the '808 patent claims a method of making copolymer-1, whereas the '589 patent claims copolymer-1 made by the same method. The same relationship is true for the applications that led to U.S. Patent No. 6,342,476 ("the '476 patent") (PTX 17) and U.S. Patent No. 6,362,161 (the '161 patent") (PTX 18).

318. The claims of the patents-in-suit were repeatedly rejected based on the '550 patent. Teva distinguished the claimed invention by noting that its "improved" invention claimed a different molecular weight range and showed unexpected results in the new range. The original patent application included, for example, a claim to "[c]opolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa." (PTX 11 at TEV000309445 (claim 4); PTX 12 at TEV000309513 (claim 4).) The PTO rejected that claim on June 26, 1995, "as anticipated by, or in the alternative, under 35 U.S.C. § 103 as obvious over Teitelbaum et al. [the '550 patent]." (PTX 12 at TEV000309541, 544, 546.) Teva did not respond to that rejection and allowed the application to go abandoned. (*Id.* at TEV000309564.)

319. Teva filed a continuation application, changing its pending claims from describing copolymer-1 with 75% of its molar fraction between 2 kDa and 20 kDa to a method of making copolymer-1 that "has a molecular weight of about 5 to 9 kDa." (PTX 13 at TEV000304135-136 (claim 20).) The PTO again rejected the claims as obvious based on the '550 patent, noting that "[t]he polymers of the prior art ['550 patent] are disclosed to have a specified minimum molecular weight of 10,000. . . ." (*Id.* at TEV000304143, 2/14/97 Office Action at 5.) Teva responded to the PTO's rejection on July 14, 1997, by arguing that:

> [T]he cited ['550 patent] reference teaches a minimum molecular weight of 10 kilodaltons. In contrast, claim 20 requires a

> copolymer-1 having a molecular weight of about 5 to 9 kilodaltons. The cited reference does not teach or suggest obtaining the claimed molecular weight fraction of claim 20. . . .

(*Id.* at TEV000304151.) The Examiner accepted this distinction and allowed claim 20 with its "about 5 to 9 kilodalton" limitation. (PTX 13 at TEV000304156 ("The examiner agrees with applicants that the prior art does not fairly suggest, teach, or disclose the subject matter embodied by claim 20.") Claim 20 became claim 1 of the '808 patent. (PTX 1.) However, before the '808 patent issued, Teva filed the application in PTX 14 with a product-by-process claim corresponding to the method claim in PTX 13. (*Compare* PTX 14 at TEV000308973 (filed February 27, 1998) *with* PTX 1 ('808 patent issued on September 1, 1998).) Teva argued that the corresponding product-by-process claim should be allowed to the same extent the PTO was going to allow the nearly identical process claim. (PTX 14 at TEV000309013.)

320. The PTO agreed and allowed the corresponding product-by-process claims without any additional rejections beyond the rejections of the method claim set forth in PTX 13. The Examiner included a "Reasons for Allowance" section in the Notice of Allowability, setting forth why the PTO was granting the product-by-process claims over the '550 patent and European Patent Application No. 0 383 620 ("the EP '620 application). The PTO specifically noted that Teva had "demonstrated unexpected results for copolymers having lower molecular weights in the instant working examples." (PTX 14 at TEV000309024.)

321. Throughout prosecution of the nine patents-in-suit, the PTO continued to reject the pending claims over the '550 patent. Examples of the rejections are included in this table:

PTX	Statement By Examiner	Response By Teva
14	"USP 3,849,550 discloses the preparation of COP-1 using the same general organic synthesis claimed herein, but does not fairly suggest or teach a molecular weight range of 5 to 9 kilodaltons." (TEV000309024)	None
15	"Claims 17-21 are rejected . . . as being anticipated by Teitelbaum et al (USP 3,849,550). Patentee discloses Copolymer-l having a preferred molecular weight range of 10,000 or more . . . . This disclosure is anticipatory of the instant claims insofar as 1) the term 'desired' is nonlimiting since no specific parameters are specifically associated with that term as instantly claimed and 2) it appears that claims 17-21 do not exclude COP-1 having a molecular weight of above 10,000 . . . . (TEV309109.)	"The cited reference teaches a minimum molecular weight of 10 kilodaltons. In contrast, the presently-claimed invention relates to a copolymer-l having over 75% of its molar fraction within the molecular weigh[t] range of about 2kDa to about 20kDa and having an average molecular weight of about 4 kDa to about 8.6 kDa." (TEV000309118.)
17	"Claims 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Teitelbaum et al (USP 3,849,550). Patentees disclose treating multiple sclerosis (column 1, line 30) with copolymer-1 having a molecular weight of more than 10,000 (column 1, line 62) but not more than 25,000 (see the fourth line of claim 1). When near the lower limit (10,000), the molecular weight limitations of instant claims 17-19 would clearly be met." (TEV000304219.)	"The presently claimed invention is directed to a method for treating multiple sclerosis, comprising . . . a pharmaceutically effective amount of a copolymer-l fraction, wherein said fraction contains less than 5% of species of copolymer-l having a molecular weight of over 40 kilodaltons; and wherein over 75% of said copolymer-l in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons. The ['550 patent] (whose authors include three of the present co-inventors) does not teach or suggest a method for treating multiple sclerosis comprising the specific copolymer-l fractions presently claimed . . . .

PTX	Statement By Examiner	Response By Teva
		The '550 patent teaches a copolymer-l with a minimum molecular weight of 10 kilodaltons. In contrast, the presently-claimed invention of independent claim 1 relates to a method wherein . . . ." (TEV000304384.)
18	"Claims 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Teitelbaum et al (USP 3,849,550). Patentees disclose compositions for treating multiple sclerosis (column 1, line 30) with copolymer-l in saline (column 2, line 37) having a molecular weight of more than 10,000 (column 1, line 62) but not more than 25,000 (see the fourth line of claim 1). When near the lower limit (10,000), the molecular weight limitations of instant claims 17-19 would clearly be met." (TEV000310336.)	"Referring now to the Office Action, claims 17-19 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 3,849,550 to Teitelbaum et al ("the '550 patent"). . . . * * * * The '550 patent teaches copolymer-l with a minimum molecular weight of 10 kilodaltons. In contrast, the presently-claimed invention of independent claim 17 . . . . (TEV000310449-50.)
19	"Claims 1-4, 7-9 and 12-14 are rejected . . . as being anticipated by Teitelbaum et al (USP 3,849,550). Patentees disclose pharmaceutical compositions for the treatment of multiple sclerosis . . . which contain COP-1 having a molecular weight ranging from more than 10KD . . . . As anyone of ordinary skill in the art will appreciate, because these are prepared by chemical polymerization . . . they will be polydisperse, i.e. they will contain a minor percentage of species above and below the target weight. When that target weight is around 10KD (or even 20KD or 25KD, as disclosed at column 2, line 22), only a very minor proportion (less than 2.5 mole percent) of species over 40KD would be present, and certainly more than 75 mole percent would be in the range of 2 to 20KD." (TEV000304448-49.)	All pending, rejected claims were cancelled. (TEV000304498.)

322. In addition to distinguishing the '550 patent based on differences in molecular weight ranges, Teva repeatedly told the PTO that its invention had demonstrated unexpected results, entitling it to patent protection. The below chart lists some arguments by Teva that the specification showed unexpected results. It also shows statements by the Examiner, indicating that it had accepted Teva's unexpected results arguments.

PTX	Statement by PTO	Response by Teva
13	"Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Teitelbaum et al (USP 3,849,550). The polymers of the prior art are disclosed to have a specified minimum molecular weight of 10,000 (column 1, line 62). As anyone skilled in the polymer art would understand, such molecular weight determinations represent an average of the molecular weights of the species in a given sample, and such sample will comprise species both above and below the specified value. Accordingly, one skilled in the art would have reasonably expected copolymer-1 of the minimum disclosed molecular weight of the prior art to have comprised at least some species within the scope of dependent claim 20." (TEV000304142-143)	"The cited reference (whose authors include three of the present co-inventors) does not teach or suggest fractionation of copolymer-1, nor suggest any advantage to obtaining particular molecular weight fractions of copolymer-1 through the claimed method. The cited reference does not teach or suggest obtaining the claimed molecular weight fraction of claim 20, nor provide a means to obtain a particular desired molecular weight fraction, as recited in claim 17." (TEV000304151-152)
17	"Claims 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Teitelbaum et al (USP 3,849,550). Patentees disclose treating multiple sclerosis (column 1, line 30) with copolymer-1 having a molecular weight of more than 10,000 (column 1, line 62) but not more than 25,000 (see the fourth line of claim 1). When near the lower limit (10,000), the molecular weight limitations of instant claims 17-19 would clearly be met.	"Applicants have demonstrated unexpectedly superior results for copolymers having lower molecular weights as shown in the examples set forth in the present application. Accordingly, applicants submit that pending claims 17, 18, 20 and 21 are not anticipated…" (TEV000304385)

PTX	Statement by PTO	Response by Teva
	Claims 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by European Patent Application 0 383 620. The prior art discloses treating multiple sclerosis (page 2, lines 5-10 and claim 13) with copolymer-1 having a molecular weight ranging from 5,000 to 50,000 (page 3, lines 8-16). When near the lower limit (5,000), the molecular weight limitations of instant claims 17-20 would clearly be met." (TEV000304219)	
18	"Claims 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Teitelbaum et al (USP 3,849,550). … Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over European Patent Application 0 383 620." (TEV000310336)	"The '550 patent (whose authors include three of the present co-inventors) does not teach or suggest a method for treating multiple sclerosis comprising the specific copolymer-l fractions presently claimed, nor suggest any advantage to a composition for the treatment of multiple sclerosis comprising the specific copolymer-1 fractions presently claimed." (TEV000310450) "Applicants have demonstrated unexpectedly superior results for copolymers having lower molecular weights as shown in the examples set forth in the present application. Accordingly, applicants submit that pending claims 17, 18, 20 and 21 are not obvious in view of the '620 application …" (TEV000310451)
19	"The determination of *optimal values* within a disclosed range is, however, generally considered obvious. … it would have been obvious to have selected a value within the molecular weight range specifically disclosed by the reference (5KD to 50KD, at page 3, line 15), including values within the	"Claims 6, 11 and 16 have been rejected under 35 U.S.C. § 103(a) as obvious over the EP reference. The Examiner states that it would have been obvious to determine optimal values within a disclosed range. The claimed range, however, shows unexpected results. As shown in Example 2, for instance, the claimed peptides have

PTX	Statement by PTO	Response by Teva
	instantly claimed range of 6.25 to 8.4KD, absent a showing of unexpected results for such selection." (TEV000304450)	unexpectedly low toxicity. Applicants therefore respectfully request withdrawal of this rejection." (TEV000304498)
20	"By contrast, Applicant has factually demonstrated that lower molecular weight Cop-1 has unexpectedly lowered side effects (see pages 5-9 of the instant specification)" (TEV000304692)	
21	"…Also, in claim 35, penultimate line, "9 kilodaltons" will be changed to the disclosed value of "about 8.6", (this concept is supported by the tenor of the specification as a whole, i.e., that the inventive copolymer-1 composition having an upper molecular weight range of about 8.6 is less toxic than copolymer-1 compositions having a greater average molecular weight." (TEV000308932)	

B. Conclusions of Law on Inequitable Conduct

323. The duty to disclose information material to patentability applied to Dr. Pinchasi.

PTO Rule 56(c) says that the duty to disclose and the duty of candor apply to:

> (1) Each inventor named in the application;
> (2) Each attorney or agent who prepares or prosecutes the application; and
> (3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

37 C.F.R. § 1.56(c) (emphasis added). Rule 56(c) applied to Dr. Pinchasi for two reasons. First, she was an originally named inventor of the patents-in-suit. (PTX 11 at TEV000309434.)

Second, she was substantively involved in the preparation of the application. (July Tr. 116:7-117:5.)

324. Rule 56(d) has a safe harbor provision that is not applicable in this case:

> (d) Individuals other than the attorney, agent or inventor may comply with this section by disclosing information to the attorney, agent, or inventor.

37 C.F.R. § 1.56(d).

325. Dr. Pinchasi is not entitled to the safe harbor for two reasons. First, on the night that the application was submitted, Pinchasi was named as an inventor. (PTX 11 at TEV000309434.) Thus, on the evening she was first accused of engaging in inequitable conduct, Dr. Pinchasi could not be described as an "individual other than the . . . inventor." Second, Dr. Pinchasi did not disclose her information to an "attorney, agent, or inventor," which is required when claiming an exemption from the duty of candor. Dr. Pinchasi testified that she gave the toxicity data to Dr. Haber. (July Tr. 122:4-7.) [redacted] Dr. Pinchasi testified that she did not remember Neil Nachshen being present the evening that the patent application was filed. [redacted]

326. Clear and convincing evidence proves that Dr. Pinchasi committed inequitable conduct on May 24, 1994.

327. To prevail on a claim of inequitable conduct, the accused infringer must prove that the patentee acted with the specific intent to deceive the PTO. *Therasense v. Becton, Dickinson & Co.*, No. 2008-1511, 2011 U.S. App. LEXIS 10590, at 24 (Fed. Cir. May 25, 2011).

Clear and convincing evidence must show that the applicant made a deliberate decision to withhold known material information. *Id.* (citations and emphasis omitted).

328. The court may infer intent from indirect and circumstantial evidence. *Id*. at *25 (citing *Larson Mfg. Co. of S.D., Inc. v. Aluminart Prods. Ltd.*, 559 F.3d 1317, 1340 (Fed. Cir. 2009).)

329. Dr. Pinchasi intentionally deceived the PTO by presenting only favorable RBL and mouse data that supported Teva's black-and-white patentability proposition that lower toxicity occurred at lower molecular weights of copolymer-1, while withholding all contradictory data that showed either no distinction or only a "probability." Dr. Pinchasi further deceived the PTO by falsely characterizing the RBL test as reproducible, when she had concluded it was not reproducible or controllable. Dr. Pinchasi consummated her deception by stating that the RBL test is useful to screen for "undesirable local and/or systemic side effects" when there was no evidence of any correlation between copolymer-1 RBL results and side effects in humans. There is no evidence that Dr. Pinchasi's selection of data and information for inclusion in the patent application was anything but intentional, and Dr. Pinchasi never corrected any of these deceptions though she remained the project manager for copolymer-1 for years after the filing.

330. "[T]he materiality required to establish inequitable conduct is but-for materiality. When an applicant fails to disclose prior art to the PTO, that prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art." *Id*. at *37.

331. If a claim is invalidated in the District Court based on the deliberately withheld evidence, then the withholding of that evidence is necessarily material because a finding of invalidity in the District Court requires clear and convincing evidence, a higher evidentiary burden than that used in prosecution at the PTO. *Id*. at *37-38.

332. However, even if the District Court does not invalidate the claims on the basis of the withheld evidence, it will still be material "if it would have blocked patent issuance under the PTO's different evidentiary standards." *Id*. at *38.

333. *Therasense's* but-for test requires the fact finder to put itself in the shoes of a hypothetical patent examiner considering the full set of facts *before* Teva was issued a patent and entitled to a presumption of validity. Before *Therasense*, the Federal Circuit recognized two "but-for" materiality standards – "the objective 'but for' standard, where the misrepresentation was so material that the patent should not have issued" and "the subjective 'but for' test, where the misrepresentation actually caused the examiner to approve the patent application when he would not otherwise have done so." *Digital Control Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1315 (Fed. Cir. 2006) (identifying materiality standards and vacating grant of summary judgment because genuine issues of material fact remained regarding materiality of withheld prior art).

334. *Therasense* did not say whether one or both of these "but-for" tests are included in its revision of inequitable conduct law. The Court should hold that proving either form of "but-for" materiality satisfies *Therasense*. A test considering only a "subjective but-for" standard would require analyzing the thought process of individual patent examiners, which would often involve a discovery exercise not permitted under PTO rules or court precedent. *See Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1363 n.4 (Fed. Cir. 1984) ("Resolution of the 'subjective but for' test is clearly factual, requiring as it does the testimony of the involved examiner with respect to the influential effect of the omitted or misrepresented information."); *W. Elec. Co. v. Piezo Tech., Inc.*, 860 F.2d 428, 431 (Fed. Cir. 1988) (recognizing general rule that a patent examiner cannot be compelled to testify regarding his "mental processes" in

reaching a decision on a patent application); *see also*, Manual of Patent Examining Procedure § 1701.01 (setting forth PTO's rule prohibiting patent examiners from testifying in court proceedings regarding patent applications and other topics).

335. While the acts of the specific Examiners in this case may be probative of what a hypothetical examiner would have done with more information, nothing the Examiner did with a less than complete data set is dispositive of the but-for test. The Court need only determine whether the PTO, correctly applying its rules, would have allowed the claims if it had been aware of the undisclosed data and misrepresentations. *Therasense*, 2011 U.S. App. LEXIS 10590, at *37. "In making this patentability determination, the court should apply the preponderance of the evidence standard and give claims their broadest reasonable construction." *Id.* In other words, if the hypothetical examiner would conclude that the preponderance of the evidence, including the information withheld from the Examiner, did not show unexpected results, the but-for test is met.

336. Teva first responded to the PTO's rejections based on the '550 patent in an Amendment made on July 17, 1997, in response to a February 14, 1997 Office Action. (PTX 13 at TEV000304138, 148-152.) The version of the Manual of Patent Examining Procedure ("MPEP") in effect at that time was the Sixth Edition, Rev. 2, July 1996 (*available at* http://www.uspto.gov/web/offices/pac/mpep/old/index.htm).) The Court may take judicial notice of and consider the MPEP to determine whether a hypothetical examiner would have allowed the claims of the patents-in-suit. *Cf. Refac Int'l, Ltd. v. Lotus Dev. Corp.*, 81 F.3d 1576, 1584 n.2 (Fed. Cir. 1996) ("The MPEP does not have the force and effect of law; however, it is entitled to judicial notice as the agency's official interpretation of statutes and regulations, provided that it is not in conflict with the statutes or regulations.").

337. At the time of that Office Action, the MPEP included a section entitled "Obviousness of Ranges."

> 2144.05 Obviousness of Ranges [R-1]
>
> * * *
>
> (a) Overlap of ranges
>
> In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) (The prior art taught carbon monoxide concentrations of "about 1-5%" while the claim was limited to "more than 5%." The court held that "about 1-5%" allowed for concentrations slightly above 5% thus the ranges overlapped). Similarly, a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corporation of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Court held as proper a rejection of a claim directed to an alloy of "having 0.8% nickel, 0.3% molybdenum, up to 0.1% iron, balance titanium" as obvious over a reference disclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium.).
>
> (b) Optimization of ranges
>
> OPTIMIZATION WITHIN PRIOR ART CONDITIONS OR THROUGH ROUTINE EXPERIMENTATION
>
> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25 and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.). *See also In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969)

> (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, *see Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804,10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989), and *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990).
>
> * * *
>
> (c) Obviousness rebuttable with secondary evidence
>
> Applicants can rebut a prima facie case of obviousness based on overlapping ranges by showing unexpected results or the criticality of the claimed range. "The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims.... In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 716.02 - § 716.02(g) for a discussion of criticality and unexpected results.

(*Manual of Patent Examining Procedure* (6th ed., Rev. 2, July 1996) § 2144.05.)

338. Section 716.02(d) would have provided an Examiner specific guidance on demonstrating criticality of a claimed range.

> DEMONSTRATING CRITICALITY OF A CLAIMED RANGE
>
> To establish unexpected results over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range. *In re Hill*, 128 USPQ 197 (CCPA 1960).

(*Manual of Patent Examining Procedure* (6th ed., Rev. 2, July 1996) § 716.02(d).)

339. A hypothetical examiner in this case would have recognized that the claimed invention was directed to copolymer-1 compositions with average molecular weights spanning claimed ranges that either overlap, lie inside, abut, or are close enough that one skilled in the art would have expected them to have the same properties. A hypothetical examiner should have

rejected the claims as prima facie obvious and shifted the burden to Teva to show unexpected results and the criticality of the claimed ranges.

340. But for the omission of the relevant data, Teva could not have rebutted a prima facie case of obviousness by establishing unexpected results in the critical range of 5 to 9 kDa or any of the other molecular weight ranges claimed in the nine patents-in-suit. Teva could not show that its claimed copolymer-1 composition and methods for making it showed unexpected results. (*See, e.g.* Section IV., *supra.*) None of the patents-in-suit would not have issued.

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APPENDIX A

Ex. No.	Batch No.	Molecular Weight	RBL %	RBL % Page
PTX-43T	24M[5]	9200 (PTX-34T at YED000002945)	35	YED000003029
PTX-43T	RE 6385	7200 (PTX-43T at YED000003029)	40	YED000003029
PTX-43T	31B	8500 (PTX-43T at YED000003029)	55	YED000003029
PTX-43T	29E	11000 (PTX-43T at YED000003028)	59	YED000003028
PTX-43T	29E-8	11000 (PTX-43T at YED000003028)	86	YED000003028
PTX-34T	430 IA HBr 2d	9000 (PTX-34T at YED000002947)	49.6	YED000002947
PTX-34T	29E	11000 (PTX-34T at YED000002947)	58.7	YED000002947
PTX-34T	27I-8	12400 (PTX-34T at YED000002946)	69.1	YED000002946
PTX-34T	29E-8	11000 (PTX-34T at YED000002947)	86.4	YED000002947
DTX-999A	24M	9200 (PTX-34T at YED000002945)	33	TEV001222396
DTX-999A	24M	9200 (PTX-34T at YED000002945)	34.0	TEV001222396
DTX-999A	24M	9200 (PTX-34T at YED000002945)	34.4	TEV001222396
DTX-999A	24M	9200 (PTX-34T at YED000002945)	36.9	TEV001222396
DTX-999A	RE 6385	7200 (PTX-43T at YED000003029)	38.9	TEV001222396
DTX-999A	24M	9200 (PTX-34T at YED000002945)	40	TEV001222396
DTX-999A	24M	9200 (PTX-34T at YED000002945)	41.7	TEV001222396
DTX-999A	RE 6385	7200 (PTX-43T at YED000003029)	41.8	TEV001222396
DTX-999A	31B	8500 (PTX-43T at YED000003029)	45	TEV001222396
DTX-999A	31B	8500 (PTX-43T at YED000003029)	46	TEV001222396
DTX-999A	31B	8500 (PTX-43T at YED000003029)	61.0	TEV001222396
DTX-999A	31B	8500 (PTX-43T at YED000003029)	69.0	TEV001222396
DTX-3477	27	8500 (DTX-3477 at TEV001084846)	12.2	TEV001084846
DTX-3477	25	12000[6] (DTX-3477 at TEV001084845)	15.4	TEV001084845
DTX-3477	365	12500[7] (DTX-3477 at TEV001084844)	25	TEV001084844
DTX-3477	320	8000 (DTX-3477 at TEV001084844)	30.2	TEV001084844
DTX-3477	32	13000[8] (DTX-3477 at TEV001084846)	30.2	TEV001084846
DTX-3317	24E2	7200 (DTX-3317 at YED000003015)	25.8	YED000003015
DTX-3317	24C2	8000 (DTX-3317 at YED000003015)	28.3	YED000003015

[5] PTX-43 uses "24M", while the translation PTX-43T uses "24N".

[6] By ultracentrifugation or viscosity.

[7] By ultracentrifugation or viscosity.

[8] By ultracentrifugation or viscosity.

Ex. No.	Batch No.	Molecular Weight	RBL %	RBL % Page
DTX-3317	24S	7200 (DTX-3317 at YED000003015)	49.0	YED000003015
DTX-3317	24U1	9500 (DTX-3317 at YED000003015)	65	YED000003015
DTX-3149	123090	7300 (DTX-3149 at TEV001222355)	21.0	TEV001222355
DTX-3149	123095	8400 (DTX-3149 at TEV001222355)	25.6	TEV001222355
DTX-3149	04792	9250 (DTX-3149 at TEV001222355)	31.3	TEV001222355
DTX-3149	123096	10950 (DTX-3149 at TEV001222355)	39.8	TEV001222355
DTX-3149	4592	11050 (DTX-3149 at TEV001222355)	41.3	TEV001222355
DTX-3149	4692	11900 (DTX-3149 at TEV001222355)	41.7	TEV001222355
DTX-3149	04492	12150 (DTX-3149 at TEV001222355)	47.6	TEV001222355
DTX-3149	4892	9600 (DTX-3149 at TEV001222355)	50.5	TEV001222355
DTX-3149	4992	9900 (DTX-3149 at TEV001222355)	51.1	TEV001222355
DTX-3149	196/2	13000 (DTX-3149 at TEV001222355)	66.9	TEV001222355
DTX-3059T	10 (RE 6203)	8000 (DTX-3059T at TEV000419252)	2.4	TEV000419252
DTX-3059T	$9A_1$ (RE 6201)	8000 (DTX-3059T at TEV000419252)	2.6	TEV000419252
DTX-3059T	12A (RE 6227)	9000 (DTX-3059T at TEV000419252)	2.6	TEV000419252
DTX-3059T	13 (RE 6228)	9500 (DTX-3059T at TEV000419252)	6.9	TEV000419252
DTX-3059T	4 (RE 6135)	10800 (DTX-3059T at TEV000419251)[9]	19.9	TEV000419251
DTX-3059T	8 (RE 6149)	11752[10] (DTX-3059T at TEV000419252)	22.5	TEV000419252
DTX-3059T	7B (RE 6151)	11000 (DTX-3059T at TEV000419252)	22.6	TEV000419252
DTX-3059T	5A (RE 6144)	10500 (DTX-3059T at TEV000419251)	24	TEV000419251
DTX-3059T	1 (RE 6117)	13000 (DTX-3059T at TEV000419251)	26	TEV000419251
DTX-3059T	13 (RE 6228)	9500 (DTX-3059T at TEV000419252)	26	TEV000419252
DTX-3059T	15A (RE 6260)	9000 (DTX-3059T at TEV000419252)	27	TEV000419252
DTX-3059T	11A (RE 6204)	11000 (DTX-3059T at TEV000419252)	27.9	TEV000419252
DTX-3059T	17C (RE-6289)	8000 (DTX-3059T at TEV000419253)	28	TEV000419253

[9] By ultracentrifugation.

[10] By ultracentrifugation.

Ex. No.	Batch No.	Molecular Weight	RBL %	RBL % Page
DTX-3059T	12A (RE 6227)	9000 (DTX-3059T at TEV000419252)	29	TEV000419252
DTX-3059T	17C (RE 6289)	8000 (DTX-3059T at TEV000419253)	30	TEV000419253
DTX-3059T	$9A_1$ (RE 6201)	8000 (DTX-3059T at TEV000419252)	35	TEV000419252
DTX-3059T	$7A_1$ (RE 6150)	11000 (DTX-3059T at TEV000419251)	35.7	TEV000419251
DTX-3059T	5A (RE 6144)	10500 (DTX-3059T at TEV000419251)	36	TEV000419251
DTX-3059T	10 (RE 6203)	8000 (DTX-3059T at TEV000419252)	37	TEV000419252
DTX-3059T	20C (RE6318)	7500 (DTX-3059T at TEV000419253)	41	TEV000419253
DTX-3059T	15A (RE 6260)	9000 (DTX-3059T at TEV000419252)	47	TEV000419252
DTX-3059T	20C (RE 6318)	7500 (DTX-3059T at TEV000419253)	52	TEV000419253
DTX-3059T	11A (RE 6204)	11000 (DTX-3059T at TEV000419252)	61	TEV000419252
DTX-3059T	$7A_2$ (RE 6452)	10500 (DTX-3059T at TEV000419252)	64.9	TEV000419252
[redacted]				

Ex. No.	Batch No.	Molecular Weight	RBL %	RBL % Page
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Ex. No.	Batch No.	Molecular Weight	RBL %	RBL % Page
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]